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THE ACTION OF ANTIBIOTICS ON *BACTERIUM COLI* INFECTIONS ASSOCIATED WITH OBSTETRICAL AND GYNAECOLOGICAL CONDITIONS

Terramycin and Combined Streptomycin and Terramycin

BY

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Infections of the urinary tract with *Bact. coli* and other organisms are now frequently amenable to therapy with sulphonamides and antibiotics. Difficulties do arise in effecting a cure, however, where abnormalities of the urinary tract are present. Furthermore, the use of certain antibiotics to which strains of *Bact. coli* are sensitive is limited. Streptomycin, for instance, though often possessing a marked bactericidal action, allows Gram negative coliform types to develop resistance rapidly when they are not immediately killed. Again, the newer antibiotics are frequently only bacteriostatic, and if a sufficient concentration is not maintained the organisms may not be destroyed.

There has been, therefore, an increasing trend recently to employ combined sulphonamide and penicillin and combined streptomycin and penicillin therapy in certain infections, including those of the urinary tract, in the hope that a more rapid and complete cure might be effected. In infections in which the organism is likely to develop resistance to a particular antibiotic the addition of another seems, on occasion, to prevent the development of the resistance. For example, terramycin has been used to prevent the development of resistance by the tubercle bacillus to streptomycin (Miller *et al.*, 1952).

Jawetz and Gunnison (1952) have made extensive studies of the use of paired antibiotics and have formulated certain conclusions. They have divided the antibiotics into 2 groups:

(1) Penicillin, streptomycin, bacitracin and neomycin, and

(2) Aureomycin, chloromycetin and terramycin.

Antibiotics of Group 1 show a higher bactericidal activity than those of Group 2 against sensitive organisms. On the other hand the antibiotics of Group 2 show a very high bacteriostatic action, often effective in extremely low dilutions, but have a weak bactericidal action. Those in Group 1 when combined in pairs have a reinforced action and are never antagonistic, while those in Group 2 can, under the same circumstances, produce only an additive action. The effect of combining drugs of different groups depends, according to the above authors, on the degree of sensitivity of the organisms. If the organism is highly sensitive to a Group 1 drug which is actively bactericidal to it, then a Group 2 antibiotic would, if added, produce interference with its action. On the other hand, if the organism is relatively resistant to Group 1 antibiotics the combination of antibiotics of both groups might produce a reinforced action. Garrod

(1953) has ably surveyed the position as regards combined therapy and has discussed the complexities which arise in determining the proper combination to be used in the treatment of a case infected with a particular organism.

It was argued, therefore, that in coliform infections of the urinary tract it might be possible to use a combination of antibiotics from Group 1 and Group 2 with greater and more specific effect than was obtained by using a single antibiotic from either group. In the first instance, as part of the bacteriological study, a series of sensitivity tests were carried out so as to demonstrate both the bacteriostatic and the bactericidal action of each of four antibiotics, streptomycin, aureomycin, chloromycetin, and terramycin, and then similar tests were applied with pairs of these antibiotics. On the information thus obtained it was decided to treat one series of cases of urinary tract infection with terramycin and another series with combined streptomycin and terramycin. Little has been published in this country on the value of terramycin therapy and nothing on combined therapy. No attempt has been made to treat a series of cases with streptomycin alone as many workers have recorded the rapid development of resistance of *Bact. coli* to this antibiotic.

I. Bacteriological Investigation

Methods

The diagnosis of urinary tract infections must be based on the clinical symptoms and investigation, and abnormal pathological and bacteriological changes. Whenever, therefore, a case was suspected to have such an infection, a specimen of urine, obtained by catheter, was submitted for the usual laboratory tests. When the causative organism was recovered, its biochemical characteristics were studied and it was tested for gross sensitivity by inoculating a blood agar plate and then applying 4 coloured blotting paper discs which had been impregnated with known concentrations of the 4 antibiotics and then dried in vacuo. After the plates were incubated overnight at 37° C. the degree of inhibition of growth was noted. Thus by using minimal concentrations for the preliminary tests little dubiety was left regarding the sensitivity of a particular strain.

As the amount of work involved in testing a strain against the individual antibiotic and paired antibiotics was very considerable this part of the investigation was limited to a study of 20 typical strains of *Bact. coli*. The methods employed in the detailed investigation of the antibiotic sensitivity of these strains were designed to demonstrate both the bacteriostatic and the bactericidal action of each drug or combination of drugs. Stock solutions of antibiotics were prepared with Messrs. Pfizers antibiotic test kit, and each stock solution containing 20,000 mcg. per ml. was kept frozen in the refrigerator until required. Prior to setting up the tests a suitable quantity of the stock solution was diluted with nutrient broth to contain 100 mcg. per ml. and then in a series of 7 sterile test tubes further dilutions were prepared by reducing the concentration by a half in each consecutive tube. By this means concentrations ranging from 100 mcg. per ml. to 1·5 mcg. per ml. were obtained. To the series of 7 tubes one drop of an actively growing broth culture obtained after incubating in broth at 37° C. for 4 hours was added. Usually 6 strains were tested in this way against two separate antibiotics, and a combination of both, at the same time. The test series of tubes were then placed in the incubator at 37° C. overnight and next morning the tubes were examined for the presence or absence of bacterial growth, the absence indicating at this stage the bacteriostatic action of the drug. The material from each tube without visible growth was then subcultured into tubes containing 3 ml. of nutrient broth to see if the organisms were still alive, and both series of tubes were then incubated for a further period of 24 hours. At the end of this period (48 hours) the antibiotic dilution tubes were re-examined for continued bacteriostasis, and subcultures were again made from tubes showing no visible growth to demonstrate the presence or absence of living organisms.

Results of Sensitivity Tests on Strains of Bact. coli

The results of the sensitivity test for the bacteriostatic and bactericidal action of each antibiotic, and combination of antibiotics, are given in Tables I and II on 20 strains of *Bact. coli*, the results being recorded after 24 hours and again after 48 hours at 37° C. Aureomycin,

TABLE I

Action of Antibiotics on 20 strains of Bact. coli

	(1) Bacteriostatic Effect No. of strains inhibited after 24 hours Micrograms per ml.							(2) Bactericidal Effect No. of strains killed after 24 hours Micrograms per ml.						
Antibiotic	100	50	25	12·5	6·25	3·1	1·5	100	50	25	12·5	6·25	3·1	1·5
Aureomycin	20	20	20	20	20	16	3	0	0	0	0	0	0	0
Chloromycetin	20	20	20	20	20	16	5	8	3	0	0	0	0	0
Streptomycin	12	9	4	2	0	0	0	12	9	4	1	0	0	0
Terramycin	20	20	20	20	20	17	4	0	0	0	0	0	0	0
Aureomycin+ Streptomycin	20	20	20	20	20	19	10	12	8	2	0	0	0	0
Chloromycetin+ Streptomycin	20	20	20	20	19	6	3	17	11	4	2	0	0	0
Terramycin+ Streptomycin	20	20	20	20	20	19	4	18	10	6	3	0	0	0
Aureomycin+ Chloromycetin	20	20	20	20	20	19	8	17	3	0	0	0	0	0
Aureomycin+ Terramycin	20	20	20	20	20	16	8	5	4	0	0	0	0	0
Chloromycetin+ Terramycin	20	20	20	20	20	20	10	14	9	9	0	0	0	0

TABLE II

Action of Antibiotics on 20 strains of Bact. coli

	(1) Bacteriostatic Effect No. of strains inhibited after 48 hours Micrograms per ml.							(2) Bactericidal Effect No. of strains killed after 48 hours Micrograms per ml.						
Antibiotic	100	50	25	12·5	6·25	3·1	1·5	100	50	25	12·5	6·25	3·1	1·5
Aureomycin	20	20	20	17	14	5	0	0	0	0	0	0	0	0
Chloromycetin	20	20	20	20	14	5	0	10	5	1	0	0	0	0
Streptomycin	12	9	4	1	0	0	0	12	9	4	1	0	0	0
Terramycin	20	20	20	18	9	4	0	2	0	0	0	0	0	0
Aureomycin+ Streptomycin	20	20	20	18	17	12	5	17	10	5	2	0	0	0
Chloromycetin+ Streptomycin	20	20	20	20	3	0	0	17	17	13	5	0	0	0
Terramycin+ Streptomycin	20	20	20	20	20	6	3	20	18	14	8	1	0	0
Aureomycin+ Chloromycetin	20	20	20	20	17	16	5	17	13	6	5	0	0	0
Aureomycin+ Terramycin	20	20	20	20	18	13	5	10	9	3	0	0	0	0
Chloromycetin+ Terramycin	20	20	20	20	20	16	6	17	14	12	4	0	0	0

chloromycetin, and terramycin were found to be effective bacteriostatic agents, though this effect at 48 hours was less than at 24 hours. At 24 hours the majority of strains were inhibited by 3·1 mcg. and many even by 1·5 mcg. per ml. As bactericidal agents all three antibiotics were much less effective and in fact aureomycin and terramycin killed no strains even in concentrations of 100 mcg. per ml., whereas chloromycetin was effective against 8 in a concentration of 100 mcg. per ml., and against 3 in 50 mcg. per ml. Streptomycin is of course in a different class, and there is little difference between its bacteriostatic and bactericidal actions. It is less effective bacteriostatically in low dilutions but is much more effective in its bactericidal action.

In paired combinations aureomycin, chloromycetin, and terramycin were more effective than if used alone, both from the point of view of bacteriostatic and of bactericidal action, though the degree of effectiveness was only in the region of a two or four-fold increase. When, however, aureomycin, chloromycetin and terramycin were each used in combination with streptomycin, both the bacteriostatic and bactericidal actions were made more effective, particularly after an exposure period of 48 hours. Terramycin and chloromycetin combined individually with streptomycin were more effective than aureomycin and streptomycin in similar concentrations. From these experiments it would seem to be justifiable to believe that in simple urinary tract infections treated with terramycin combined with streptomycin effective cure could be established in a short time provided the organism did not develop rapid resistance.

Inhibition and prevention of resistance of Bact. coli *to Streptomycin by Terramycin*

In view of the results obtained in inhibiting the development of resistance when terramycin was given in combination with streptomycin in the

TABLE III

Resistance of Subcultures to Streptomycin after Repeated Subculture in Antibiotics compared with Action on Control Cultures

		Bacteriostatic Effect 24 hours mcg. per ml.									Bactericidal Effect 24 hours mcg. per ml.								
Strain	Subculture	12·800	6·400	·	50·	25·	12·5	6·25	3·1	1·5	12·800	6·400	·	50·	25·	12·5	6·25	3·1	1·5
1	Control	0	0	·	0	0	0	0	0	+	0	0	·	0	0	0	0	+	+
	S	0	0	·	0	0	0	+	+	+	0	0	·	0	0	0	+	+	+
	T	0	0	·	0	0	0	0	+	+	0	0	·	0	0	0	+	+	+
	S & T	0	0	·	0	0	0	+	+	+	0	0	·	0	0	0	0	+	+
5	Control	0	0	·	0	0	0	0	0	+	0	0	·	0	0	0	+	+	+
	S	0	0	·	0	0	0	+	+	+	0	0	·	0	0	0	+	+	+
	T	0	0	·	0	0	0	0	+	+	0	0	·	0	0	0	+	+	+
	S & T	0	0	·	0	0	0	+	+	+	0	0	·	0	0	0	0	+	+
6	Control	0	0	·	0	0	0	0	0	+	0	+	·	+	+	+	+	+	+
	S	0	+	·	+	+	+	+	+	+	0	0	·	0	0	0	0	+	+
	T	0	0	·	0	0	0	0	+	+	0	0	·	0	0	+	+	+	+
	S & T	0	0	·	0	0	+	+	+	+	0	0	·	0	0	0	0	+	+
11	Control	0	0	·	0	0	0	0	0	+	0	+	·	+	+	+	+	+	+
	S	0	+	·	+	+	+	+	+	+	0	0	·	0	0	0	+	+	+
	T	0	0	·	0	0	0	0	+	+	0	0	·	0	0	+	+	+	+
	S & T	0	0	·	0	0	+	+	+	+	0	0	·	0	0	0	0	+	+
20	Control	0	0	·	0	0	0	0	0	0	0	0	·	+	+	+	+	+	+
	S	0	0	·	0	+	+	+	+	+	0	0	·	0	+	+	+	+	+
	T	0	0	·	0	0	0	0	+	+	0	0	·	0	0	0	0	+	+
	S & T	0	0	·	0	0	0	0	+	+	0	0	·	0	0	0	0	+	+

S = Streptomycin
T = Terramycin
S & T = Streptomycin and Terramycin

Treated Culture 0 = no growth
+ = growth

treatment of infections due to tubercle bacilli, it was thought necessary to see if this also happened when strains of *Bact. coli* were subjected to a similar influence.

Accordingly, 5 strains of *Bact. coli* markedly sensitive to the action of both streptomycin and terramycin were chosen for test purposes. A series of three sets of cultures of the 5 strains were grown in broth containing a weak dilution of the antibiotics. The first series of passages were made in broth (brain heart infusion) containing 2 mcg. per ml. of streptomycin; 5 mcg. of terramycin; and a combination of 2 mcg. and 5 mcg. of streptomycin and terramycin respectively. After an incubation period of 24 hours the tubes were examined for bacteriostatic action and then if no growth was visible a loopful was taken from each tube and incubated into another tube containing 3 ml. of broth. This new set of tubes were then incubated for a further period of 24 hours and the bactericidal action of the antibiotics determined.

In the first test the antibiotics were not found to be bactericidal so for the second passage the amounts of the antibiotics present in the broth were increased slightly and the procedure described above was repeated. As the process was continued with increasing amounts of antibiotic it was often found that too much antibiotic, particularly streptomycin, had been employed so recourse had frequently to be made to cultures surviving from lower dilutions. The bactericidal action of streptomycin was particularly noticeable when it was combined with terramycin. Eventually, after a series of 18 passages over a period of 2 months, a re-examination of the original strains and all subcultures was made for their resistance to both streptomycin and to terramycin. All the final tests with streptomycin were carried out at one time and so also all the final tests with terramycin.

The results of these experiments are summarized in Tables III and IV. In the first place it should be noted that the original control

TABLE IV

Resistance of Subcultures to Terramycin after Repeated Subculture in Antibiotics Compared with Action on Control Cultures

Strain	Subculture	Bacteriostatic Effect 24 hours mcg. per ml.							Bactericidal Effect 24 hours mcg. per ml.						
		100	50	25	12·5	6·25	3·1	1·5	100	50	25	12·5	6·25	3·1	1·5
1	Control	0	0	0	0	+	+	+	+	+	+	+	+	+	+
	S	0	0	0	+	+	+	+	+	+	+	+	+	+	+
	T	0	0	+	+	+	+	+	+	+	+	+	+	+	+
	S & T	0	0	0	0	0	+	+	+	+	+	+	+	+	+
5	Control	0	0	0	0	0	0	0	+	+	+	+	+	+	+
	S	0	0	0	0	0	0	0	+	+	+	+	+	+	+
	T	0	0	0	0	0	0	+	+	+	+	+	+	+	+
	S & T	0	0	0	0	0	0	+	+	+	+	+	+	+	+
6	Control	0	0	0	0	0	0	0	+	+	+	+	+	+	+
	S	0	0	0	0	0	0	0	+	+	+	+	+	+	+
	T	0	0	0	0	0	+	+	+	+	+	+	+	+	+
	S & T	0	0	0	0	0	0	+	+	+	+	+	+	+	+
11	Control	0	0	0	0	0	0	+	+	+	+	+	+	+	+
	S	0	0	0	0	0	0	+	+	+	+	+	+	+	+
	T	0	0	0	0	0	0	+	+	+	+	+	+	+	+
	S & T	0	0	0	0	0	0	+	+	+	+	+	+	+	+
20	Control	0	0	0	0	0	0	+	+	+	+	+	+	+	+
	S	0	0	0	0	0	0	0	+	+	+	+	+	+	+
	T	0	0	+	+	+	+	+	+	+	+	+	+	+	+
	S & T	0	0	0	+	+	+	+	+	+	+	+	+	+	+

S = Streptomycin
T = Terramycin
S & T = Streptomycin and Terramycin

Treated Cultures 0 = no growth
+ = growth

cultures of the 5 strains of *Bact. coli* which had been set aside for 2 months showed, when retested, no increased resistance to the bacteriostatic or bactericidal action of streptomycin and terramycin.

In the series of 5 subcultures which had been subjected to culture in gradually increasing amounts of streptomycin 2, Nos. 6 and 11, acquired a massive resistance to the extent of being able to grow in 6,250 mcg. per ml. but not in 12,500 mcg. per ml., whereas the control cultures of the same organisms only grew in 1·5 mcg. per ml. and not in 3 mcg. per ml. Another strain, No. 20, acquired resistance to 50 mcg. per ml. whereas the control was only resistant to 1·5 mcg. per ml. The other 2 strains 1 and 5 developed only slight resistance and were found to be able to survive in 6·25 mcg. per ml.

In the case of the 5 subcultures which had been repeatedly cultured in terramycin, resistance to the bacteriostatic action was increased slightly in 2 strains, since they were able to grow in concentrations of 25 mcg. per ml., whereas the control cultures grew only in concentrations of 6·25 and 1·5 per ml.

In the series treated with combined streptomycin and terramycin it was found difficult to grow the organisms in increasing concentrations of the antibiotics, but after 18 passages the results, summarized in Table V, were obtained.

TABLE V

Comparison of Bactericidal Effect of Streptomycin Greatest Amount in mcg. per ml. Permitting Growth

Strains	Control Series	After 18th passage through Streptomycin alone	After 18th passage through combined Streptomycin and Terramycin
1	3·1	6·25	6·25
5	3·1	6·25	6·25
6	1·5	6250	12·5
11	1·5	6250	6·25
20	1·5	50	3·1

In this series, therefore, the combination of terramycin with streptomycin must have had an inhibitory effect on the development of resistance to streptomycin. As explained, it was difficult to passage the organisms through increasing concentrations since the powerful bacteriostatic action of the terramycin seemed to enhance the bactericidal effect of streptomycin.

II. Antibiotic Therapy of *Bact. coli* Infections of the Urinary Tract

The ideal treatment of any infection is to use the drug which will be most effective, have least toxicity, and cost least. It has also to be borne in mind that not only does resistance develop to a specific antibiotic, but that cross resistance also occurs against those drugs which have a similar antibacterial spectrum. This is particularly liable to occur where there is poor contact between the drug and the infecting organism, as in a collection of pus, or where dosage is inadequate. Again there is the equally important fact that bacteria may come to depend on an antibiotic such as streptomycin for growth (Miller and Bohnhoff, 1947). This can be demonstrated both in vitro and in vivo, and indeed certain organisms have their growth enhanced by the presence of streptomycin.

In the papers which reported a high percentage of failures in the treatment of urinary infections there was almost invariably a reason. In most cases it was due to stasis of urine caused by pathological abnormalities, by calculi, and by malignant disease. In such cases it is inevitable that any treatment will have but a temporary effect on the urinary infection, and that reinfection will occur. The rational approach is initial treatment with a suitable antibiotic followed shortly after by surgical treatment directed towards the correction of the pathological process. Indeed, to delay surgical treatment will in some cases promote the formation of strains of organisms which are resistant to antibiotics.

The Urinary Excretion of Antibiotics

In urinary infections in particular, a drug should be used which attains a high concentration in the urine and at the same time has an adequate concentration in the tissues. This is necessary to destroy organisms which may remain in the kidney substance or in other foci of infection. Each of the antibiotics so far in general

use is excreted in substantial amounts in the urine. In fact on only a moderate dosage high concentrations can be obtained. Most authorities agree that 50 to 70 per cent of streptomycin given parenterally is excreted. Gould *et al.* (1952) give figures of the percentage excretion of an oral dose over a 6-hourly period. Their mean percentage figures for control subjects and patients were:

Penicillin	80
Streptomycin	20
Chloramphenicol	3·4
Aureomycin	27
Terramycin	7·5

Schoenbach *et al.* (1950) stated that 11 to 15 per cent of the total dose of oral terramycin could be recovered and Welch *et al.* (1950) found that terramycin, given orally in single or multiple doses, gave a greater concentration in the urine than either aureomycin or chloromycetin. Linsell and Fletcher (1950) found that with terramycin even on a dosage as low as 10 mg. per kilogram of body weight a concentration of 10 mcg. per ml. could be obtained. Welch *et al.* (1950) with a dosage of 0·5 grams q.i.d. obtained 140 mcg. per ml. of urine, with 1 gram q.i.d. 300 mcg. per ml., and with 2 grams 400 mcg. per ml. Werner *et al.* (1950) intimated that most of a single dose of chloromycetin excreted in the urine is in a biologically inactive form, but about 7 per cent was excreted in a biologically active form. The active form of recoverable terramycin was also about 7 per cent but that of aureomycin was significantly less, only 4 per cent.

The investigations of Finlay *et al.* (1950) and Hobby *et al.* (1950) of the activity of terramycin in vitro suggest this antibiotic to be the drug of choice in most urinary infections. It is relatively free from toxic qualities (Schoenbach *et al.*, 1950) and used where there is renal damage it will not aggravate the condition (Pemrick, 1950). A further point in its favour is that the efficiency of the drug is not influenced by variation in the reaction of the urine (King *et al.*, 1950). Terramycin is rapidly absorbed from the gastrointestinal tract and widely distributed throughout the body. Maximum blood concentration is attained within 2 hours. Excretion of terramycin in the urine begins within half an hour of oral administration and about 15 per cent of the total dose can be recovered from the urine within 24 hours. These high concentrations of the antibiotic in the urine are of significance in the treatment of urinary tract infections.

Terramycin and Combined Streptomycin and Terramycin in the Treatment of Urinary Tract Infections

Already there are many reports on the general use of terramycin in urinary tract infections, and in most instances satisfactory results are recorded. Blake *et al.* (1950) found that coliform and other infections responded promptly. McKenzie and Nugent (1950) selected for therapy 41 cases in which many other antibiotics and drugs had been used and failed. Approximately two-thirds of these complicated resistant cases showed an excellent or good response to terramycin. The only report of the treatment of pyelitis and of pregnancy cysto-ureteritis came from Douglas *et al.* (1950), and here again the response to treatment was good, since 26 out of the 32 cases investigated responded satisfactorily. Bickel and Plattner (1951) found that 9 out of 10 cases responded satisfactorily. Nesbit *et al.* (1951) carried out an exacting evaluation of this antibiotic on patients who had long standing infections and who had had much previous therapy with various sulphonamides and other antibiotics. It is significant that 20 out of 24 cases so treated showed prompt improvement but 10 relapsed when the drug was withdrawn. Womack *et al.* (1952) reported a series of 112 acute and chronic cases of urinary tract infection treated with terramycin in 37 per cent of which the urine was rendered sterile. In this unusual series there were 14 deaths and the most important feature of the fatal cases was the frequent occurrence, during terramycin therapy, of infection due to resistant strains of haemolytic *Staphylococcus aureus*. The secondary infections included pneumonia, endocarditis, and dysentery all due to the *Staph. aureus*. A serious aspect of terramycin therapy in the fatal cases was the vomiting and diarrhoea which accompanied the administration of the drug, the diarrhoea and vomiting being severe enough to interfere with the further, or adequate, administration of the drug. They believed that these symptoms were the major

contributing factors to the fatal outcome. Gould *et al.* (1952) reported a series of 23 male patients with urinary tract infections. Many of the patients had complicating factors such as calculi or indwelling catheters. The total dosage of terramycin was usually 10 g. The results in this trial were poor as only 2 of the 25 patients had sterile urine at the end of the course of treatment. Many of the failures were due to a rapid development of resistance of the organisms to terramycin.

This brief review of the literature shows that the results of terramycin therapy were on the whole satisfactory, though there were quite frequent failures.

The literature on the use of streptomycin in urinary tract infections is extensive. Garrod (1950) in a review of the uses of this antibiotic stated, at that time, that streptomycin was the most potent of all urinary antiseptics. A short course was often most effective but on the other hand there was always the possibility that coliform organisms would develop resistance. Anderson (1953), in a discussion on antibiotics, stated streptomycin should never be used in urinary tract infections because bacterial resistance developed so rapidly. As regards the use of combined terramycin and streptomycin no reports are available, but the results of our bacteriological investigation have indicated that for *Bact. coli* infections the combination is most useful.

Cases and Therapy

It was decided to treat the first 25 cases of *Bact. coli* infection with terramycin and a second group of 27 with streptomycin and terramycin. It was possible that some infections following certain obstetrical and gynaecological conditions might be more difficult of radical cure than others, but as it took a considerable time to collect the series it was considered advisable not to select the cases in any way. The types of cases treated and their distribution are given in Table VI. Only 4 cases of pyelitis of pregnancy were available and only 6 with pre-operative gynaecological conditions. The majority of the infections were post-operative occurrences and therefore were fairly acute and less likely to produce clinical failures. In this post-operative group most cases were associated with repair operations for prolapse, 12 occurring in the terramycin treated series and 16 in the combined antibiotic series. Generally speaking, therefore, the cases in each series were fairly comparable.

Table VI

Classification of Cases Treated with Antibiotics

Condition	No. treated with Terramycin	No. treated with combined Antibiotics
Obstetrical—antepartum ..	3	1
postpartum ..	—	2
Gynaecological—pre-operative		
Prolapse and diabetes	1	—
Prolapse	—	1
Stress incontinence	2	1
Endometriosis	—	1
Gynaecological—post-operative		
Prolapse—repair	10	13
Prolapse—vaginal hysterectomy	2	3
Stress incontinence—repair ..	1	—
Fibroids—hysterectomy ..	3	—
Endometriosis—ovariotomy ..	1	2
Pyo-salpinx—salpingectomy ..	1	—
Carcinoma of cervix—radium—Wertheim hysterectomy ..	1	—
Cervicitis—amputation ..	—	1
Menorrhagia—D. & C. ..	—	1
Post-menopausal haemorrhage D. & C.	—	1
	25	27

In the first series of cases, the dosage of oral terramycin was 0·5 g. 6-hourly for 72 hours, followed by 0·25 g. 6-hourly for another period of 72 hours. In the second series of cases 0·5 g. of oral terramycin was given 6-hourly for 3 days and 1 g. of streptomycin was given twice daily parenterally for the same period, the urine during this course being maintained in an alkaline condition. At the conclusion of treatment and after a period of 48 hours or more had been allowed to elapse since the final dose of drug had been given, further catheter specimens of urine were collected for microscopic and bacteriological examination.

Results

In the group of patients treated with terramycin alone, there was a quick response to treatment by the majority, and in most the

symptoms associated with urinary tract infections had begun to subside within 24 or 48 hours after therapy had been started. In fact in all, except 1, the urine had become sterile after the prescribed course. In this series there were 3 cases which had been previously treated with sulphonamides, and even these responded to terramycin. In the second series, treated with combined streptomycin and terramycin, the results were still more successful as there were no failures in therapy. Not only was this so, but with the combined antibiotic the onset of improvement in the clinical condition of the patients usually occurred within 12 hours of starting treatment and at an earlier stage than when terramycin alone was given, even in 4 cases who had previously failed to respond to sulphonamides. Fever, discomfort and frequency subsided within 12 hours and the urinary specimens were in most cases clear and free from inflammatory exudates within 24 hours. Furthermore, in 4 cases it was found that when a course of treatment was started late at night and a catheter specimen of urine obtained next morning, these urines were sterile, and the patients had had at the most only 2 doses of the combined antibiotic. The actual difference from the point of view of cure between the two series of cases was not marked, but with the shorter course of combined antibiotic therapy, the rapidity with which cure was effected was particularly noticeable.

As regards side effects from the use of antibiotics, these were relatively unimportant. In the terramycin treated series 3 cases complained of abdominal discomfort, some nausea and diarrhoea, and 1 complained of pruritus ani. In the series treated with the combined antibiotics the short course seemed to lessen the possibility of reaction and only 1 complained of mild abdominal discomfort.

Discussion

There can be no doubt that for the treatment of infections, including those of the urinary tract, many chemo-therapeutic agents with remarkable properties are now available. The difficulty, however, is to select the drug, or combination of drugs, which will be the most effective in dealing with a particular organism. In this study attention has been confined to *Bact. coli* infections of the urinary tract associated with obstetrical and gynaecological conditions. It has been confirmed that terramycin is an effective bacteriostatic agent in vitro and also in vivo for *Bact. coli*, but it lacks the additional merit of being bactericidal. Streptomycin, as has been shown many times before, is a bactericidal agent and, if not bactericidal in a particular dilution, will not be bacteriostatic either. The in vitro experiments have shown quite definitely that a reinforced action can be obtained by using a combination of both these antibiotics, and this seems to have been borne out by the therapeutic trials, since the patients so treated gave a more immediate response than those treated with terramycin alone. The difficulty about the use of streptomycin has been the development of resistance, particularly in the Gram-negative group of organisms, but the in vitro experiments have indicated that the development of resistance can be inhibited by combining it with terramycin, and there is no reason to suppose that this effect would not also be manifest in the tissues of the human body. Whatever may be the eventual explanation, metabolic or genetic, for the development or inhibition of resistance of a bacterium to an antibiotic, the main point is the practical application of therapeutic measures to overcome infection.

Summary

(1) In vitro experiments have shown that terramycin has a markedly bacteriostatic but little bactericidal action on all strains of *Bact. coli* tested.

(2) In similar experiments the bacteriostatic and bactericidal effects of streptomycin were found to be almost identical.

(3) Certain strains of *Bact. coli*, when passaged in broth cultures through increasing amounts of the antibiotics, developed slow resistance to terramycin but often marked resistance to streptomycin.

(4) When the same strains of *Bact. coli* were passaged in broth cultures containing combined antibiotics the development of resistance was inhibited.

(5) Clinical tests showed that terramycin was

an effective chemo-therapeutic agent in infections of the urinary tract.

(6) Further clinical tests showed that the use of the combined antibiotic was even more effective, and that a shorter course of therapy could be given.

(7) The side effects arising from the use of the antibiotics were of negligible importance.

ACKNOWLEDGMENTS

Thanks are due to Professor W. I. C. Morris for permission to treat patients in his Obstetrical and Gynaecological Units, and for his encouragement. To Messrs. Pfizer and Co. we are indebted for generous supplies of terramycin.

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HORMONAL ASSESSMENT BY VAGINAL CYTOLOGY

BY

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THE determination of whether and when a patient is ovulating is a problem often encountered by the gynaecologist. It is met with in sterility clinics and in gynaecological as well as endocrine patients. Methods at present in use are either time consuming, e.g., Farris's test on Wistar rats (1950), necessitate admission to hospital, e.g., for endometrial biopsies, or meet with difficulties in interpretation, e.g., biochemical assessments and basal temperature charts.

For these reasons we tried to evaluate the hormonal balance as indicated by exfoliated cells from the posterior fornix. Similar studies have been carried out in the Argentine by De Allende and Orias (1950) and in Belgium by Paul Pundel (1950) but the method so far has not been adopted as a routine technique.

As the essential point is the assessment of the daily hormonal output, the method necessitates the daily collection of material. Therefore, we instructed our patients on how to take their own smears and supplied them with portable apparatus. This reduced their hospital attendance to one weekly visit and the estimations could then be done simultaneously. The patients proved extremely co-operative and in no case were unsuitable smears presented.

Hormonal assessment was carried out during the past 18 months on 15 adult patients; 2 of these showing an initial anovulatory cycle were done repeatedly. Ovulation or failure to ovulate was confirmed by endometrial biopsy and daily temperature charts were kept for comparison.

The method is based on two criteria:

(*a*) A simple count of the cornified cells, expressed as a percentage of all squamous cells (cornification index or C.I.) under the assumption that cornification is a function of oestrogenization.

(*b*) The presence of the typical cyclical patterns, especially the occurrence of progesterone effects in the secretory phase 24 to 48 hours after the characteristic ovulatory picture. In fact, only the clustering of cells, the edge curling of the individual cell and the accompanying influx of leucocytes and micro-organisms together with a sharp drop in the C.I. are proof of ovulation. The ovulatory pattern is produced by a high oestrogen level and can, therefore, be simulated by oestrogen administration or abnormal oestrogen production without ovulation as occurs in the presence of a follicular cyst (Figs. 1, 2, 3).

The cornification index in a normal ovulatory cycle shows a steady rise in the proliferative phase with a peak value at ovulation and a sharp fall as the corpus luteum starts functioning. There may be a secondary rise during the secretory phase but this never reaches the level of the peak value.

Comparing the charts from various patients, we soon found that there are distinct types of curves which are diagnostic of certain endocrine entities. There are:

(*a*) The normal ovulatory curve characterized by its typical shape (Fig. 4). This was taken from

a 28-year-old patient with regular menstruation. She complained of sterility the cause of which was never ascertained and which was, as the hormonal pattern and biopsy proved, not due to failure of ovulation. Fig. 5 shows a similar curve without the secondary rise of C.I. during the secretory phase. This was taken from a 35-year-old woman with secondary sterility. Ovulation was confirmed by subsequent endometrial biopsy. She has since conceived and was delivered of twin boys.

(*b*) The erratic curve which shows no uniform pattern and is best described as an uncoordinated and frustrated attempt at oestrogen production.

Fig. 6a illustrates this very well. This curve comes from a 37-year-old woman and was taken during an anovulatory cycle. Follow-up cytology in a subsequent month revealed a normal ovulatory curve which was confirmed by an endometrial biopsy (Fig. 6b).

Fig. 7 comes from a 28-year-old woman who complained of irregular periods with intervals of amenorrhoea of 2-3 months' duration. Subsequent biopsy confirmed failure of ovulation.

(*c*) The inactive curve which is flat without any attempt at cyclical hormone production and which denotes a severe impairment of ovarian function. Consecutive smears of normal postmenopausal women and prepubertal girls show an identical type of curve.

Fig. 8 comes from a 32-year-old patient attending the endocrine clinic who complained of very irregular periods and hirsutism. No ovarian activity was demonstrated by vaginal cytology.

Fig. 9 is an almost identical curve from a 20-year-old patient in a mental hospital with primary amenorrhoea.

Fig. 10 was taken from a post-menopausal woman aged 65.

No other type of curve was found in any of the patients studied, but South American authors (De Allende and Orias, 1950) describe a fourth type which they claim as diagnostic of a follicular cyst. This pattern is a flat curve with a high level C.I. without a secretory drop in the oestrogen content.

We found that C.I. and general pattern seemed to be correlated to a certain extent. Whereas the cells found in patients with normal ovulatory curves are of the superficial squamous type, smears of patients with erratic or inactive curves consist mainly of intermediate squames and have a high proportion of basal cells. As an example of the practical value of cytologic hormonal assessment the following case history is briefly recorded:

L.M., age 30 years, para 2+1, attended the Gynaecological Outpatients' Department complaining of amenorrhoea of 2 years' duration. Her menstrual history was grossly irregular. Vaginal bleeding occurred at the age of 15 years, lasting for 1 day only; thereafter no further vaginal loss followed until shortly after marriage, at the age of 25 years. This was an apparently normal period, but coincided with the commencement of her first pregnancy which ended 8 months later, in January, 1948, with the delivery of a normal baby at term. Six weeks after the birth of the child, regular cyclical bleedings at 4 weeks' interval occurred until her second pregnancy began in October, 1948, which ended by spontaneous abortion in March, 1949. Thereafter menstruation recurred regularly until her third pregnancy in 1949. A full time normal infant was born in May, 1950. For the next 7 months menstruation was again regular until December, 1950. No further periods were seen until a scanty 1-day bleeding in September, 1952, when the patient attended the hospital.

Clinical examination revealed no abnormality. Hormonal assessment by vaginal cytology gave the interesting result shown in Fig. 11 from 2 consecutive cycles. Not only were normal ovulation and normal progesterone effects demonstrated, but a microscopic cyclical bleeding with the pattern usually observed in normal menstruation was also observed. Subsequent endometrial biopsy taken on the 17th day of the cycle (as postulated by smear findings) showed a normal secretory endometrium.

Comment

This case report shows that prolonged amenorrhoea does not necessarily indicate a low oestrogen state in the body nor even an incapacity for ovulation and conception.

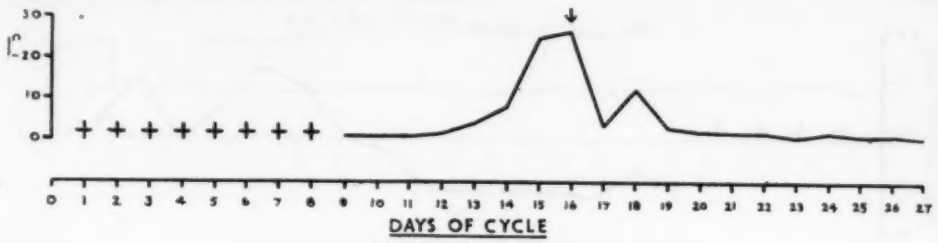

FIG. 4

Normal ovulatory curve.

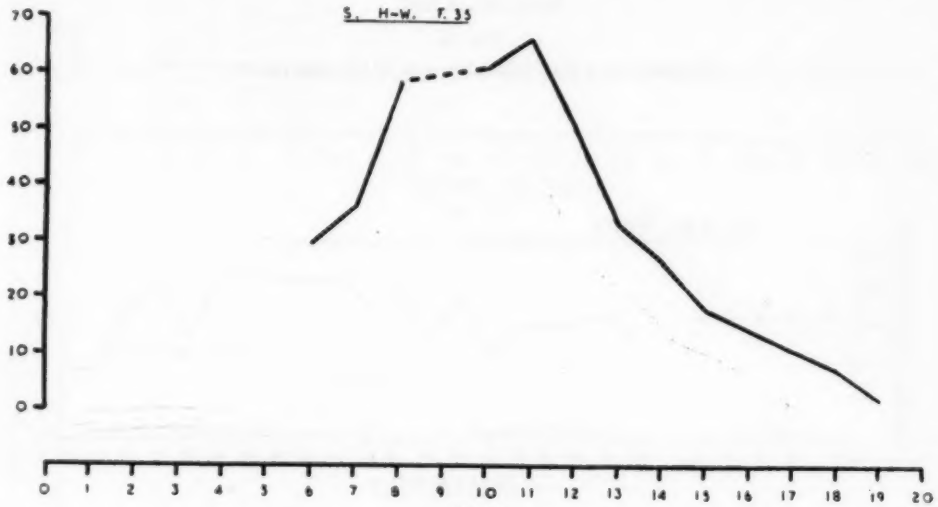

FIG. 5

Normal ovulatory curve without secondary rise in cornification index.

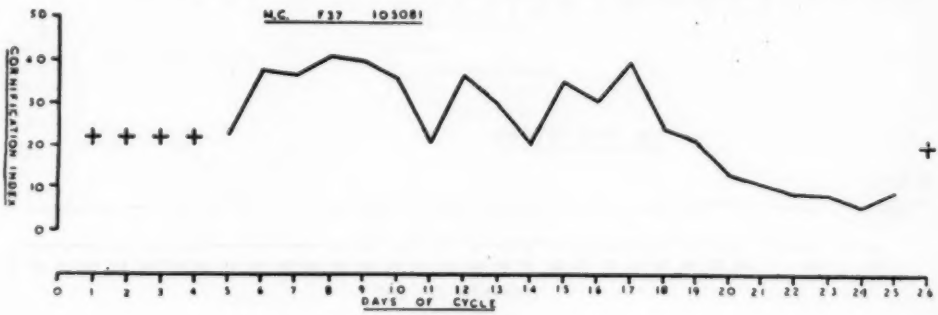

FIG. 6a

Erratic curve (anovulatory).

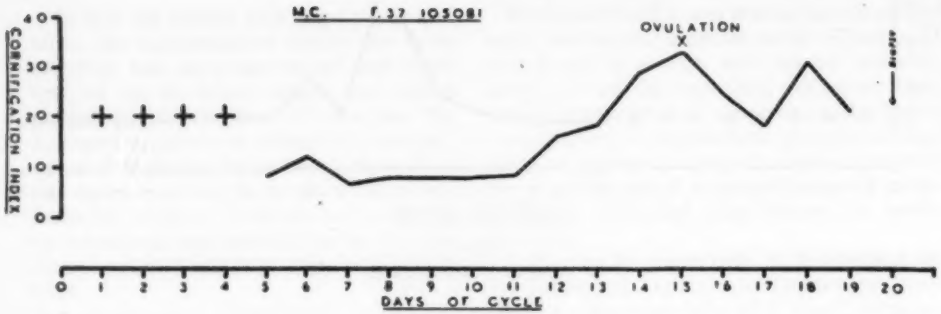

FIG. 6b

Ovulatory curve from subsequent cycle of the same patient.

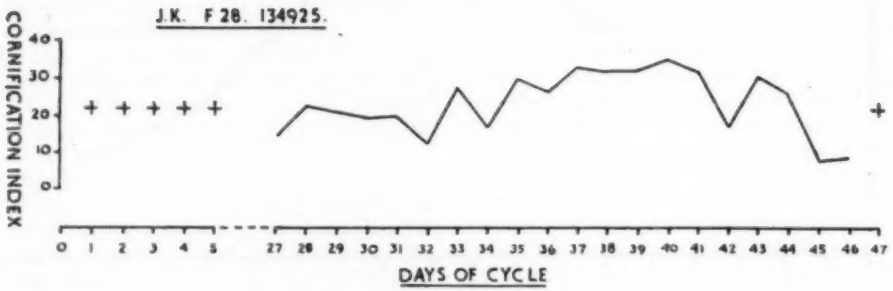

FIG. 7

Erratic anovulatory curve.

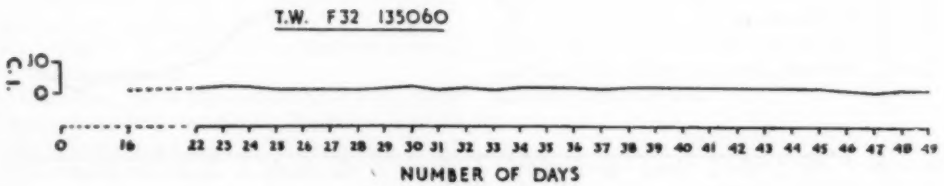

FIG. 8

Atrophic curve from a patient with irregular periods.

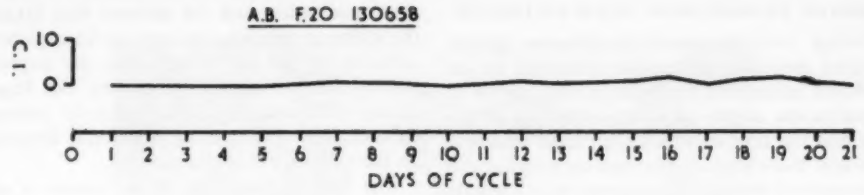

FIG. 9

Atrophic curve from a patient with primary amenorrhoea

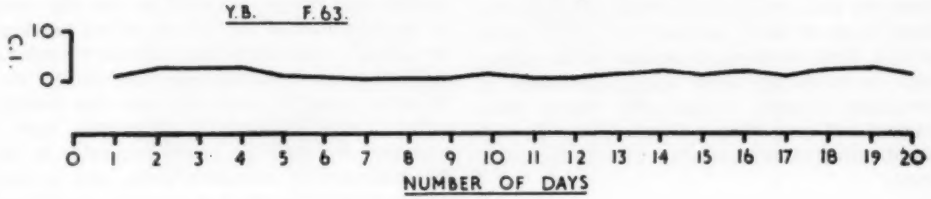

FIG. 10

Atrophic curve from a post-menopausal woman.

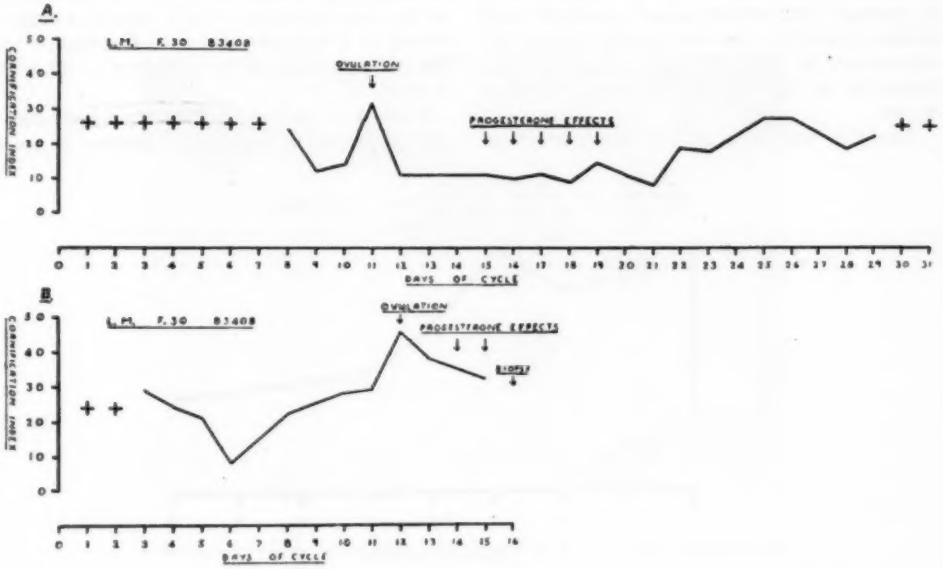

FIG. 11

Two normal ovulatory curves from a patient complaining of secondary amenorrhoea (see text).

Hormone Estimations in Newborn Infants

During our hormonal studies on gynaecological patients, we became interested in the hormonal balance of newborn infants, trying to determine the degree of oestrogenization of the baby and the time in which the excess maternal oestrogen was excreted. We were surprised at the uniformity of the curves obtained in 10 female babies studied. Fig. 12 is a graph of the average figures obtained from daily vaginal smears in the first week of life.

We also studied 4 male infants, taking smears from the oral cavities and found essentially the same shape of curve, although on a lower level of C.I. This, however, is ascribed to the difference in technique rather than a difference in oestrogen content. Comparative curves, both vaginal and oral, from a female infant showed an identical pattern and the same difference in level.

Discussion

We found daily smears a useful method of determination of hormonal balance as well as ovulation. It is sufficient to continue the curve in patients with problematical ovulation until definite secretory signs are present; failing the appearance of these, the curve should be continued for at least 28 days or until a bleeding occurs.

The C.I. was regarded as the criterion of oestrogenization and no account was taken of the staining reaction. In contrast to continental authors, we do not believe that the degree of acidophilia, in smears stained by the Papanicolaou technique, is a true index of oestrogen balance, since the staining reaction is dependent on the varying pH of the vagina.

The interpretation of these curves is quite simple. It is easy to say whether a patient has ovulated and it is possible, in retrospect, to say when ovulation has occurred. It is, however, essential to realize that smear patterns and cornification indices obtained on one day refer to the condition of the patient on the previous day; since it takes about that time for the cells to exfoliate and collect in the posterior fornix. We, therefore, wish to stress the fact that cornification curves are only a diagnostic help *a posteriori*, but have no prognostic value in the determination of ovulation time, and in fact do not even tell us whether ovulation is likely to occur.

Similar considerations apply to the oestrogen curves obtained in newborn infants. The seemingly unexpected peak of oestrogenization on the second full day of life is really a logical finding as it corresponds to the flooding of the infant's circulation with oestrogens at the time of birth.

Failures of this type of oestrogen determination are mainly caused by the presence of gross

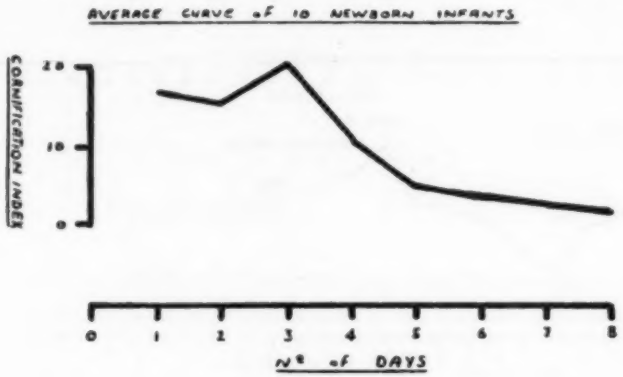

Fig. 12

Average oestrogen curve of 10 newborn infants.

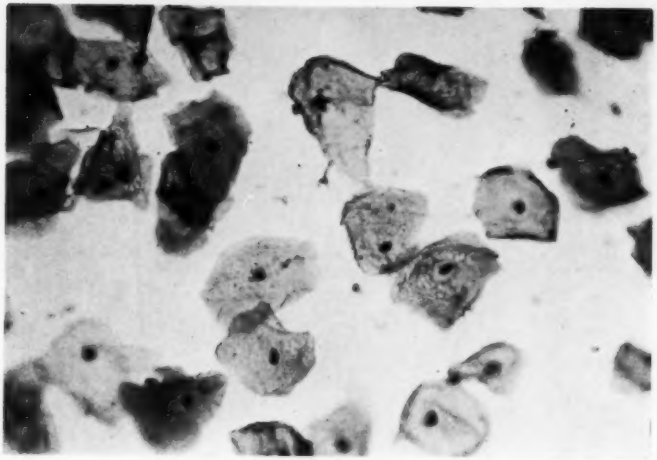

FIG. 1
Ovulatory pattern.

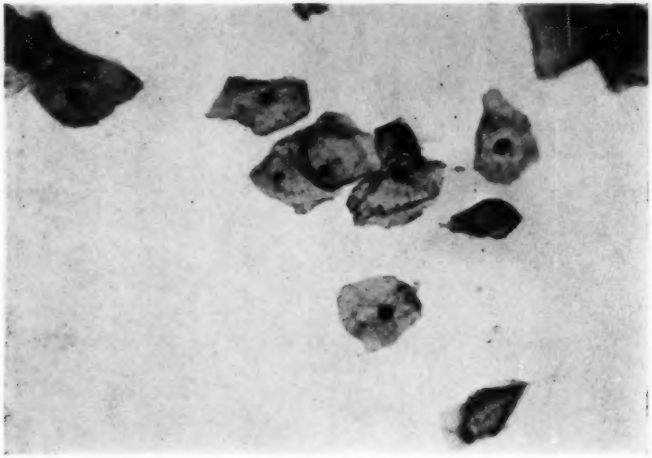

FIG 2
Simulated ovulatory pattern in a post-menopausal woman receiving oestrogens.

FIG. 3
Secretory phase.

infection and hormone estimations should not be carried out in such cases. Certain infections, e.g., *Trichomonas vaginalis*, may affect the degree of cornification irrespective of the hormonal balance, and any deep infection destroying surface epithelium accounts for the presence of basal cells in vaginal smears, which could be misinterpreted.

We regard the shape of the curve as more important than the actual height of the peak value. It may be of interest that Inez de Allende (1950) mentions average peak values of C.I. in normally ovulating women between 45 and 90 per cent, whereas our mean values are much lower than this, averaging between 30 and 50 per cent. Whether this is an essential racial or climatic difference or due to difference in interpretation cannot be decided.

Summary

A simple cytological technique of determination of ovarian function is described. Cytological patterns and cornification curves of different patients regarded as diagnostic, are illustrated and discussed.

Acknowledgments

Our thanks are due to Professor J. C. McClure Browne, Mr. Charles Read, Mr. Ian Donald and Mr. J. D. Murdoch for permission to publish these case histories. In addition we wish to thank Mr. Murdoch for his helpful criticism and advice on the preparation of this paper. We also wish to thank Mr. E. V. Willmott of the Postgraduate Medical School of London for the photomicrographs.

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FOETAL ANOXIA

BY

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A Clinical and Laboratory Study

The Blair-Bell Memorial Lecture, September, 1953, delivered at The Royal College of Obstetricians and Gynaecologists, London

"And in the womb of a mother was I moulded into flesh.
Within the space of ten months, . . ."
Wisdom of Solomon, VII, 1, 2.

I WISH to thank the Council of the College for the honour they have conferred upon me in the award of a Blair-Bell Memorial Lectureship.

My subject is perhaps appropriate, as, in 1928, the late Professor Blair-Bell, in co-operation with colleagues in Liverpool, published the first recorded readings of the oxygen content of the blood in the umbilical vessels in the human foetus.

The foetus depends for its growth and development on an adequate supply of nutrients from the mother. Oxygen is unique amongst those, as it cannot be stored and the supply must be ample and continuous. Even a moderate deficiency over a short period may seriously injure the foetus (Ingalls *et al.*, 1950). Near term the human foetus can survive a total lack of oxygen for a period of about 30 minutes, provided its circulation is intact, and lesser degrees of anoxia for longer periods. It is doubtful, however, if it will always escape completely unharmed, as the higher cerebral centres are less resistant than the more primitive centres directly responsible for survival (Darke, 1944; Brinkman, 1953).

OXYGEN SUPPLY TO THE HUMAN FOETUS

Several important factors are concerned in maintaining the supply of oxygen to the foetus. The maternal arterial blood must be adequately saturated with oxygen and the maternal general circulation normal. The blood vessels to, and in the uterine wall must grow and develop normally in response to the pregnancy. The placenta should be normally grown and the deciduo-placental site fully developed and healthy. The layers of the foetal villus between the two bloods should function normally, and the circulation in the umbilical cord must not be impeded. Maternal blood pours into the intervillous spaces and oxygen is transferred by diffusion to the foetal blood.

Circulation of the maternal blood through the placenta in late pregnancy and labour depends on regular uterine contractions. Inadequate or prolonged contractions or a high resting tone may interfere with this circulation. In the foetal vessels circulation depends mainly on the action of the foetal heart.

All those factors govern the amount of oxygen reaching the foetus, and disease processes of many kinds may interfere. Even, however, in the absence of disease, the oxygen supply undergoes a series of changes as pregnancy progresses. This was first demonstrated by Barcroft and his colleagues in the goat (1934) and the sheep (1939).

Very little is known about the levels of oxygen supply to the human foetus before the onset of labour. What information there is, is confusing, and the conclusions drawn are contradictory (Eastman, 1930; Haselhorst and Stromberger, 1930, 1931; Dieckmann and Kramer, 1944). No studies have been made of possible variations of oxygen supply during normal pregnancy, or in association with abnormal clinical states.

I felt that it would be worth while to study the oxygen levels in the blood of the human foetus at abdominal and vaginal delivery in the latter

half of pregnancy, before and after labour, and in normal and abnormal cases. The problem is really one of human physiology, but it seemed an ideal investigation for a clinician to undertake, as a detailed experience of the clinical features of pregnancy and labour is essential in the interpretation of the results.

Methods

For all cases studied there was a detailed clinical history and the length of gestation was accurately known. Spinal or local anaesthesia was used for all operative deliveries studied, because inhalation anaesthetics interfere with most techniques of blood-gas analysis (Shaw and Downing, 1935). They may, in addition, interfere with the oxygen supply to the foetus (Smith, 1939; Taylor *et al.*, 1951).

I took all blood samples myself and was present during delivery in all cases. Thus, difficulty in delivery could be assessed, the state and response of the baby noted, and samples could be obtained accurately and quickly. All oxygen estimations were made as quickly as possible and always within 6 hours. The method used, that of Roughton and Scholander (1943), could be applied at short notice, and was accurate with close agreement of duplicate readings.

At an early stage in the work, it became apparent that there was a close relationship between haemoglobin and oxygen levels in the cord blood, and Dr. Elizabeth Turnbull was appointed as a Research Fellow to assist in the haematological side of the enquiry.

Oxygen Levels before the onset of Labour

An account of the changes in the oxygen levels in the blood of the vessels of the umbilical cord of the human foetus in the second half of normal pregnancy has been recently published (Walker and Turnbull, 1953). The readings given there were obtained at abdominal delivery under spinal anaesthesia before the onset of labour.

In normal pregnancy the oxygen content of the blood in the umbilical vein appears to fall slowly from 14 vols. per cent at or about the 30th week till the 39th or 40th week when it is about 12 vols. per cent. The fall thereafter is very rapid, and by the 43rd week the content is less than 8 vols. per cent. Since the foetus normally takes 6 to 7 vols. per cent the fall of the content in the artery parallels that in the vein. At the 43rd week the foetus is just able to get enough oxygen from the blood for its needs in a resting state, and returns little or no oxygen to the placenta. There is, therefore, at this stage, no reserve to compensate for any other factor which might interfere with the oxygen supply. When the supply begins to fall, the foetus attempts to maintain the content by increasing the oxygen-carrying power of its blood, that is, it produces more haemoglobin. This attempt at acclimatization might succeed if the oxygen supply were stable at a new low level, but it is only of limited value to the foetus, as the supply at source continues to decrease and the haemoglobin vainly keeps on rising till, at the 43rd week, it may be as high as 140 per cent. As the content continues to fall and the haemoglobin continues to rise, the blood is becoming less and less saturated with oxygen, as more haemoglobin is carrying less oxygen. The per cent saturation, that is, the amount of oxygen carried relative to the amount which could be carried, is therefore the best measure of the efficiency of the oxygen supply, as it will only begin to fall when the haemoglobin rises in response to anoxia. The per cent saturation is also a better measure than the content of the oxygen available to the foetal tissues, since the tension or head of pressure in the blood is related closely to the per cent saturation. For these reasons, therefore, the oxygen supply reaching the foetus before and after labour will be discussed mainly with reference to the per cent saturation with oxygen of the blood in the umbilical vessels. Content and capacity findings are available in the relevant tables.

The per cent saturation of the blood in the umbilical vein in the latter half of normal pregnancy is 70 per cent at or about the 30th week, 60 per cent at 39 or 40 weeks, and falls to under 30 per cent at 43 weeks. All babies are not, however, even as well oxygenated as this, and the blood of some infants in apparently normal pregnancy is only 30 to 40 per cent saturated even at 40 weeks. A deficient oxygen supply may therefore be seen at any time in the last few weeks of pregnancy, but by the 42nd to 43rd week the supply is dangerously low in almost all

foetuses. Where the pregnancy is complicated by pre-eclampsia, or if abortion has threatened earlier in the pregnancy, the oxygen supply may fail sooner than in normal cases (Walker and Turnbull, 1953).

Oxygen Levels in the Cord Blood after Labour

Oxygen levels in the cord blood at the moment of birth have been studied by many investigators (Eastman, 1930; Haselhorst and Stromberger, 1930; Noguchi, 1937). It is generally agreed that the well-oxygenated infant begins life with its blood about 50 per cent saturated with oxygen. I have shown, however, that the per cent saturation with oxygen of the blood in the umbilical vessels before the onset of labour varies with the week of delivery, and at 42 to 43 weeks most infants begin labour with the blood in the umbilical vein less than 40 per cent saturated.

After *easy spontaneous delivery* the oxygen levels in the cord blood are seen in Table I and Fig. 1. These cases were delivered without analgesia, and there was no evidence of the passage of meconium by the foetus. In Fig. 1 the per cent saturation of the blood in the umbilical vein of the individual cases is plotted against the range of readings found by Walker and Turnbull (1953) to be normal before the onset of labour. It is seen that the readings after delivery all fall close to the range of readings found before labour begins provided comparisons are made at the same week of gestation. It is only to be expected that a physiological process like normal labour should have little effect on the oxygen supply to the foetus.

After *prolonged or difficult labour*, where the foetus is born in a severe state of asphyxia, very low levels of oxygen are found in the cord blood (Eastman, 1932; Wilson *et al.*, 1937), but no

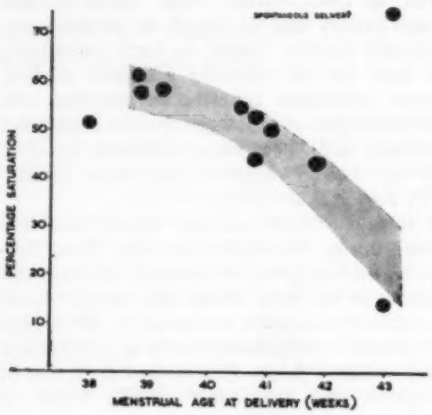

FIG. 1

Per cent saturation with oxygen of blood in the umbilical vein at spontaneous delivery (without evidence of meconium staining).

TABLE I

Oxygen Levels in Umbilical Vessels
Spontaneous Delivery without Anaesthesia and without evidence of Meconium Staining

Case No.	Menstrual Age (weeks)	Duration Labour (hours)	Oxygen Capacity Vols. per cent	Oxygen Content in Vols. per cent		Per cent Saturation	
				Vein	Artery	Vein	Artery
412/51	38	19	23·8	11·9	0·7	50·0	2·4
2001/52	39	38	19·8	11·8	5·4	60·0	28·0
2821/52	39	9	22·4	12·7	5·4	57·0	24·0
1642/52	39	17	21·8	12·4	6·2	56·9	28·5
827/51	41	12	22·0	12·2	—	55·3	—
806/51	41	7	23·0	11·7	6·3	50·9	27·6
805/51	41	12	23·1	12·2	6·6	52·8	28·8
813/51	41	14	20·6	8·9	3·6	42·8	17·4
2728/52	42	13	23·6	10·4	4·5	44·0	19·0
1597/51	43	11	23·8	3·2	0·2	13·4	0·9
		Mean ..	22·4	10·7	4·3	48·3	19·6

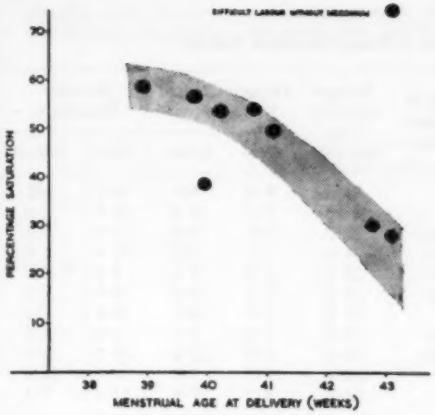

FIG. 2

Per cent saturation with oxygen of blood in the umbilical vein after prolonged or difficult labour (without evidence of meconium staining).

evidence is available of the likely effect of difficult labour itself.

In Table II are seen the oxygen levels in the blood of the cord vessels in a series of infants born after labours lasting from 11 to 89 hours, and ending with operative delivery under spinal anaesthesia. There was, however, no evidence of meconium in the liquor. In Fig. 2 the readings of the per cent saturation with oxygen of the blood in the umbilical vein are plotted against the range of readings found to be normal before the onset of labour. It is seen that there is little or no difference when compared with the levels found before the onset of labour. In the absence of meconium, therefore, the oxygen supply to the foetus during prolonged or difficult labour does not appear to be interfered with to any extent.

During prolonged or difficult labour, however, the foetus frequently shows clinical evidence of distress, the liquor is heavily stained with meconium, and at birth the infant's skin may be covered with a golden-green film. The oxygen levels in such cases are usually very low.

Recent meconium staining. The oxygen levels in a series of cases where the foetus had recently passed meconium in labour or was found to be covered with meconium at delivery are seen in Table III. In Fig. 3 the readings of the per cent saturation of the blood in the umbilical vein are plotted against the range found to be normal before the onset of labour. Two important points are seen.

(*a*) The per cent saturation of the blood in the umbilical vein is at or below 30 per cent no matter the stage of gestation.

(*b*) This level of 30 per cent, the "distress level", as I call it, is around the level of oxygen supply at which most foetuses in the 43rd week normally begin labour.

The information shown by Tables II and III and Figs. 2 and 3 suggests that prolonged or difficult labour may have only little effect on the

TABLE II

Oxygen in Blood of Umbilical Vessels in Difficult Labour without evidence of Meconium

Case No.	Menstrual Age (weeks)	Type of Delivery	Duration Labour (hours)	Oxygen Capacity Vols. per cent	Oxygen Content Vols. per cent		Per cent Saturation	
					Vein	Artery	Vein	Artery
2969/50 ..	39	Low Forceps	17	24·2	13·9	5·3	57·3	22·0
525/51 ..	40	Low Forceps	19	21·6	11·6	1·0	53·9	4·1
1651/51 ..	40	Diff. Mid Forceps	55	23·1	8·6	2·8	37·1	12·2
2820/52 ..	40	Diff. Mid Forceps	89	22·2	12·1	6·0	55·0	27·1
2765/50 ..	41	Mid Forceps	11	19·8	10·0	4·0	50·4	20·1
3124/50 ..	41	LUCS	21	24·2	13·3	7·3	54·8	30·0
506/51 ..	43	Diff. Mid Forceps	46	24·8	6·8	3·6	27·6	14·5
3027/52 ..	43	LUCS	34	23·4	6·5	0·9	28·0	4·0
			Mean ..	22·9	10·4	3·9	45·5	16·8

TABLE III

Oxygen in the Umbilical Vessels when there is Recent Meconium Staining

Case No.	Menstrual Age (weeks)	Type of Delivery	Duration Labour (hours)	Degree of Meconium Staining	Oxygen Capacity Vols. per cent	Oxygen Content Vols. per cent		Per cent Saturation	
						Vein	Artery	Vein	Artery
2683/50 ..	40	LUCS	32	Light	21·8	6·6	Nil	30·2	Nil
667/53 ..	41	LUCS	94	Light	27·2	7·5	1·5	28·2	5·0
2995/50 ..	41	LUCS	12	V. Heavy	22·2	3·9	0·9	17·6	4·0
1596/53 ..	42	LUCS	Elect.	V. Heavy	24·6	7·7	1·5	31·4	6·0
5/52 ..	43	LUCS	114	V. Heavy	25·2	2·0	0·9	8·0	3·6
1447/51 ..	43	LUCS	18	V. Heavy	23·2	4·3	0·5	18·7	2·0
2291/51 ..	43	LUCS	49	Light	25·8	5·4	0·7	20·8	2·6
991/51 ..	43	LUCS	62	Moderate	25·6	3·0	0·7	11·6	2·6
3054/52 ..	43	LUCS	35	Moderate	25·6	6·6	2·0	25·8	7·8
1506/51 ..	43	S.D.	16	Light	24·6	7·5	3·7	30·6	11·9
3001/51 ..	43	LUCS	Elect.	Light	25·6	8·2	1·9	32·1	7·4
				Mean ..	24·7	5·7	1·3	23·2	4·8

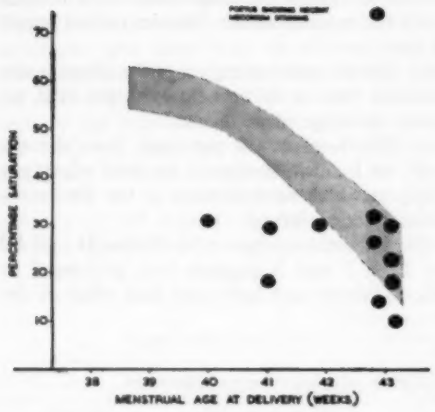

FIG. 3

Per cent saturation with oxygen of blood in the umbilical vein where the foetus has recently passed meconium.

oxygen supply to the foetus, and that this deficiency can be easily met by the oxygen reserve of the well-oxygenated baby. Where, however, the oxygen supply is already deficient and at or near distress levels, meconium staining will be likely to occur during labour. Conversely, if an infant during labour does pass meconium, it is likely to have begun labour with an already deficient oxygen supply, and this state of affairs is likely to be more common in the 42nd and 43rd weeks.

Summary of Oxygen Findings

(1) The oxygen supply to the human foetus in a clinically normal pregnancy falls gradually up to the 40th week and rapidly thereafter.

(2) Most foetuses at 40 weeks are well oxygenated and have nearly 100 per cent reserve, but in some the supply is low, and the reserve is correspondingly reduced.

(3) The number of foetuses with a poor oxygen supply increases in the next few weeks until, by the 43rd week, all foetuses have a low oxygen supply and practically no reserve. They are forced at the best to clear all oxygen from their blood to obtain enough for their resting needs.

(4) The well-oxygenated baby can stand the effect of labour of any kind without becoming short of oxygen, but the foetus, already with a deficient supply, is likely to experience deficiency of oxygen during labour and to declare this deficiency by passing meconium.

(5) When meconium is passed, the saturation of the blood in the umbilical vein is at or below 30 per cent, and the foetus is not obtaining enough oxygen to survive indefinitely.

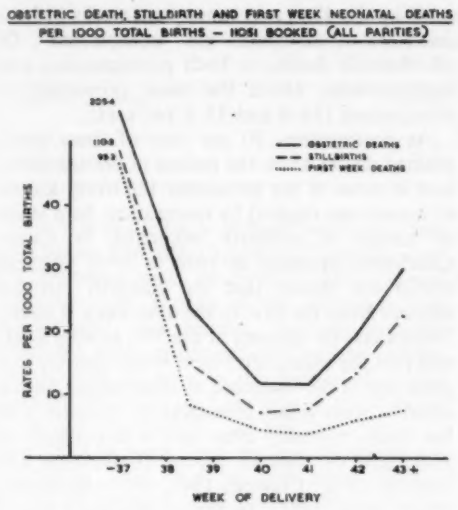

FIG. 4

Obstetric Death, Stillbirth, and first-week Neonatal Death Rates per 1,000 total births.

CLINICAL EFFECTS OF ANOXIA

Since oxygen deficiency becomes more common and more severe after term, one might expect to find, after that time, an increasing incidence of foetal deaths due to anoxia, and a greater incidence of clinical evidence of distress during labour.

Obstetric Death

In Fig. 4 are seen the obstetric death, stillbirth and first-week neonatal death rates per 1,000 total births in relation to the duration of pregnancy in 11,051 booked patients of all parities, delivered from 1948 to 1952. The obstetric death rate is 11·7 and 11·5 for deliveries in the 40th and 41st weeks, but rises steadily thereafter till for deliveries at or after the 43rd week it is 28·5. The rise in rate after 41 weeks is due mainly to a rise in stillbirths as has been shown by others (McKiddie, 1949; Gibberd, 1952), but it is seen that the first-week death rate rises from 3·8 at the 41st week to 7·1 for deliveries in the 43rd and subsequent weeks. The risk of neonatal death is definitely greater for the post-mature infant than for the infant delivered during the 40th or 41st weeks.

Fig. 5 shows that the rise in the death rate after the 40th and 41st weeks is due primarily to a rising incidence of unexplained deaths, that is, death of the foetus where no clinical abnormality of pregnancy or labour was present which might

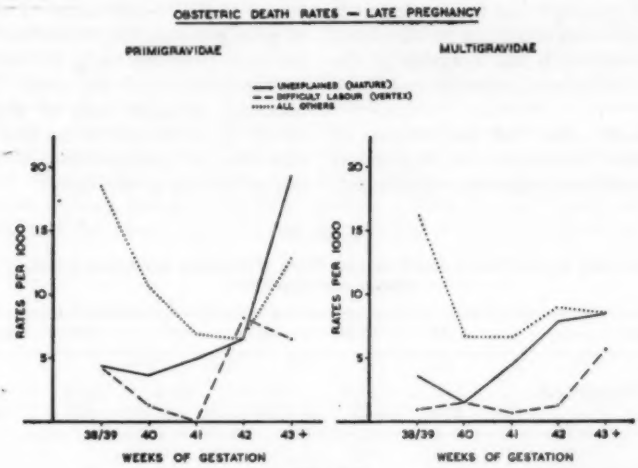

FIG. 5

Obstetric Death Rates in late pregnancy by clinical cause of death.

explain why the baby died. Deaths of this type are uncommon at 40 to 41 weeks, but by 43 weeks in primigravidae and in multigravidae they are the highest single cause of death. In primigravidae, there is also a rise in incidence of deaths considered to be directly due to difficult labour (in infants presenting by the vertex). The death rate from "other causes" is also raised in the 42nd and 43rd weeks. This is not surprising as the anoxic foetus is less likely to be able to withstand the further anoxic effects of pre-eclampsia, cord prolapse or breech delivery.

In the above series, it is possible to calculate death rates in each week as the duration of pregnancy of most patients delivered over the 5-year period 1948-1952 is accurately known. Exclusion of obstetric deaths in cases where the gestational age is uncertain does not influence the shape of the curves (most are in premature foetuses). The actual number of deaths, however, is small, and some of the curves are of doubtful statistical significance (see Note on p. 179). In view of this, all stillbirths and first-week deaths occurring in 10,785 primigravidae and 12,723 multigravidae booked for and delivered in the Aberdeen Maternity Hospital from 1938 to 1951 have been studied and a clinical cause assigned to each death. The proportion of deaths from each cause in relation to the total deaths occurring at each week of gestation has been calculated. Death rates at each week could not be calculated as accurate information is not available of the gestational age of all infants delivered over those years.

Table IV shows that the proportion of "unexplained deaths" (in babies over 5½ pounds) is seen to rise steadily as pregnancy is prolonged, until by the 42nd and subsequent weeks at least one-third of all deaths are "unexplained". Of all obstetric deaths in both primigravidae and multigravidae, about the same proportion is unexplained (14·4 and 12·8 per cent).

At postmortem, 70 per cent of these unexplained deaths show the lesions of anoxia alone, and in most of the remainder the likely lesions of anoxia are masked by maceration. In a study of causes of stillbirth occurring in Queen Charlotte's Hospital in 1948 to 1950, Gibberd (1952) has shown that the stillbirth rate for delivery from the 41st to the 45th week is nearly 3 times that for delivery at the 37th to 40th week, and that the excess after term is due entirely to a great rise in the incidence of unexplained anoxic deaths. Most other investigators consider that the excess mortality after term is due mainly to prolonged or difficult labour (Ballantyne and Browne, 1922; Clayton, 1941, 1953; Rathburn, 1943; Latto, 1951). In this connexion I would like to stress that, if a foetus dies of anoxia early in the first stage of a labour which lasts for 3 days and ends with a difficult forceps delivery, the death must surely be classified as "unexplained", and not as due to prolonged labour or traumatic delivery.

In Table V, however, is seen the proportion of deaths assessed as directly due to difficult labour in the 13-year series. It will be noted that in primigravidae the proportion of deaths (14·0 per cent) from this cause is much higher than in multigravidae (4·3 per cent). The proportion occurring in each week of gestation is fairly steady up to the end of the 41st week, but after that time, in primigravidae, 37·1 per cent of all deaths are due to this cause.

TABLE IV

Proportion (per cent) of all Obstetric Deaths at each Stage of Gestation which were Clinically Unexplained (Babies over 5½ pounds)

Week of Delivery	−37	38-39	40	41	42+	Uncertain	Total
Primigravidae							
Per cent Deaths Unexplained ..	1·7	11·3	16·7	24·4	32·4	15·0	14·4
Total Deaths	173	71	30	45	105	40	464
Multigravidae							
Per cent Deaths Unexplained ..	1·8	19·6	11·5	30·2	35·6	11·1	12·8
Total Deaths	228	56	26	53	59	45	467

TABLE V

Proportion (per cent) of all Obstetric Deaths which are due to Difficult Labour (Vertex presentation only) (Total Deaths as in Table IV)

Week of Delivery	−37	38-39	40	41	42+	Uncertain	Total
Primigravidae	—	15·5	16·7	15·5	37·1	—	14·0
Multigravidae	—	5·0	11·5	11·1	13·6	—	4·3

Obstetric death due to difficult labour is of two main types. The first, "traumatic", usually seen in association with mechanical difficulty and associated with tearing of the tentorium and haemorrhage; the second, "anoxic", usually associated with prolonged dysfunction labour and showing at autopsy the lesions of anoxia alone. At 40 weeks 13·3 per cent of all obstetric deaths are "traumatic", 3·3 per cent "anoxic". After the 41st week 13·3 per cent of deaths are "traumatic", but 23·8 per cent are "anoxic". The rise in rate and proportion of deaths due to difficult labour after term is thus seen to be due mainly to a rise in deaths from anoxia. Death from anoxia in association with difficult labour is extremely uncommon until after term, and 83 per cent of all such deaths occur after the end of the 41st week.

The Incidence of Difficult Labour

The rise in incidence of deaths directly due to difficult labour is to some extent explained by the increasing incidence of difficult labour after term. Normal labour is defined as spontaneous vertex delivery in under 24 hours, and all other labours are "difficult". Major difficult labours are those with undue prolongation of labour with deterioration of maternal condition, or Caesarean section or difficult forceps extraction because of the nature of the labour itself. (Cases of malpresentation, Caesarean section or forceps for foetal distress, maternal disease, etc., are excluded.) In Table VI it is seen that the incidence of difficult labour in primigravidae rises steadily from the 37th to the 44th weeks. The rise is due entirely to an increasing incidence of a major degree of difficulty. At the 40th week only 3·1 per cent of all cases have a major degree of difficulty in labour or delivery, but by the 44th week the figure rises to 13·7 per cent. This rise is due mainly to an increase in uterine dysfunction of severe degree, but mechanical difficulty also increases and is made clinically more important by the less efficient contractions.

The importance of a rising incidence of difficult labour after term has been noted previously by Rathburn (1943), DeLee and Greenhill (1947), Beruti and Roust (1948), Reenkola (1948), Stewart (1952), and Clayton (1953).

Clinical Evidence of Foetal Distress

The findings shown earlier in this paper confirm the importance of anoxia as a cause of obstetric death after the 40th week of gestation, but all anoxic foetuses do not die, and more information can be obtained from a study of foetal distress. For the purposes of this investigation I have defined foetal distress as gross irregularity of the foetal heart, or slowing to or

TABLE VI

Per cent Incidence of Difficult Labours (Vertex Delivery) in Primigravidae

Week of Delivery	−37	38-39	40	41	42	43	44+	Uncertain	Total
All Difficult Labour	15·4	19·9	24·2	29·8	32·3	35·5	34·5	21·8	25·9
All Major	0·8	3·5	3·1	6·7	9·4	13·0	13·7	2·7	5·7
Minor	14·6	16·4	21·1	23·1	22·9	22·5	20·8	19·1	20·2
Cases at Risk	254	573	693	813	501	200	58	412	3,504

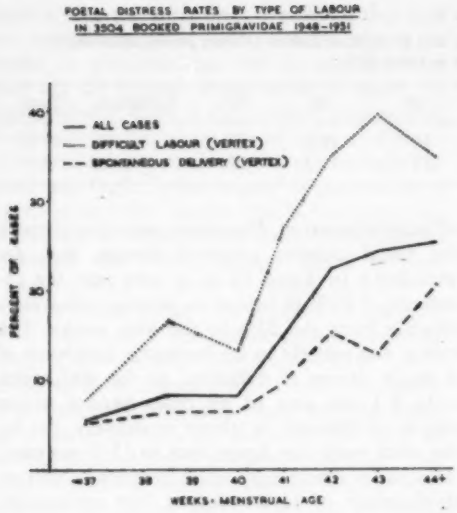

FIG. 6

Foetal Distress rates in various types of labour in primigravidae.

below 100 beats per minute, or the passage of meconium in presentations other than breech. According to the oxygen findings, it would appear that the foetus will pass meconium only when it is short of oxygen. Aetiologically, cases of distress therefore fall into two main groups, those where meconium is passed, and those where heart signs are present alone.

The incidence of foetal distress in all labours is seen in Fig. 6. It is low before and at the 40th week, at which time only 8·4 per cent of babies show distress. The rate rises steadily till at the 44th week evidence of distress is shown in 25·9 per cent of labours. In "normal" labours the rate is only a little lower, the rise beginning in the 41st week and by the 44th week it is 21·1 per cent. The distress rate in cases of difficult labour (vertex presenting) is, however, high. At 40 weeks 13 per cent of foetuses undergoing difficult vertex labour show clinical evidence of distress, and, at the 43rd week, 39·4 per cent.

Incidence by Clinical Cause. Each clinical history has been studied and a clinical cause assigned to the distress. In Fig. 7 it is seen that the incidence from all causes is low up till the 40th week (in primigravidae). When distress is due to prolonged labour or to pressure on the foetal head in the pelvis (combined in Fig. 7) the rising incidence after term is due to a great extent to the rising incidence of difficult labour after that time. Distress due to cord complications rises in incidence since the anoxic foetus is less able to withstand interference with the cord circulation. Distress occurring late in the second stage (slowing of the foetal heart) with the head on the perineum is somewhat more frequent after that time. The most marked and constant rise, however, is in those cases of distress clinically unexplained, and after the 41st week this is the greatest single "cause" of distress (10·5 and 10·3 per cent of all cases at the 43rd and 44th week respectively).

In multigravidae, distress rates rise also after the 40th week, but in view of the greatly diminished incidence of difficult labour it is not valid to compare the total incidence of distress with that in primigravidae. In Fig. 8 the incidence of cases of distress clinically "unexplained" is seen in primigravidae and in multigravidae. The behaviour and incidence with prolonged

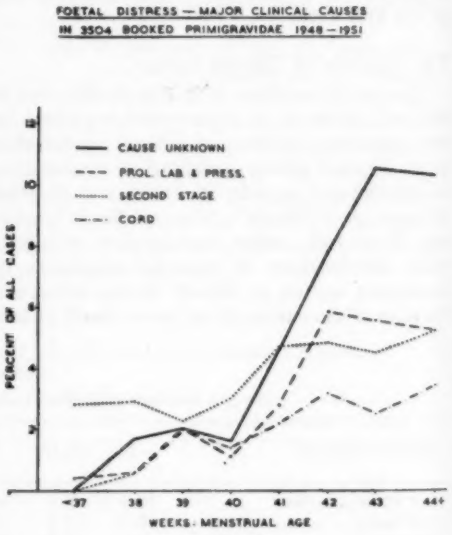

FIG. 7

Foetal Distress rates in all labours by clinical cause of distress.

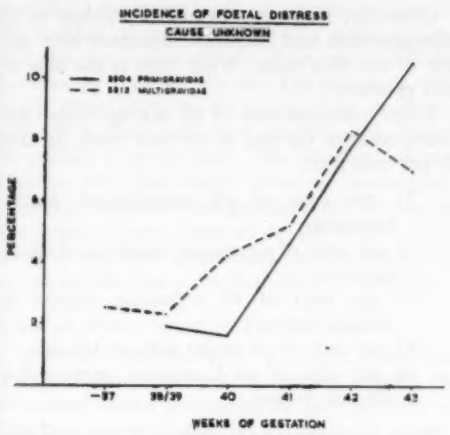

FIG. 8

Incidence of foetal distress of unexplained or unknown cause.

pregnancy are similar. In 95 per cent of cases of distress which are clinically unexplained the foetus has passed meconium, and Fig. 8 really demonstrates that the incidence of "unexplained" meconium staining, which is "unexplained" anoxia, rises equally and behaves similarly in all parities as pregnancy becomes prolonged.

Summary of Statistical Findings. The conclusions that may be drawn from the statistics presented are as follows:

(1) The obstetric death rate is 3 times as high at 43 weeks as it is at 40 weeks, because of an increase in stillbirths.

(2) This increase is due mainly to a rise in incidence and proportion of unexplained deaths.

(3) There is, in primigravidae, also a rise in the incidence and proportion of deaths due to difficult vertex labour, but the increase is mainly because of many more deaths from anoxia and only in small part because of an increase of cerebral birth trauma.

(4) The incidence of foetal distress rises sharply after 40 weeks. In primigravidae the rise is partly explained by an increase in distress associated with the rising incidence of difficult labour. In both primigravidae and multigravidae, however, the main factor in the rise is a great increase in the incidence of cases showing meconium staining which, though clinically unexplained, is due probably to a marked deficiency in the oxygen supply to the foetus.

THE CLINICAL PROBLEM

Experimental and statistical evidence suggests strongly that the fall in the oxygen supply to the human foetus in late pregnancy is the main factor in the rising stillbirth rate after 40 weeks, and in the greatly increased incidence of foetal distress in labour. The passage of meconium (in presentations other than breech) is evidence that the foetus is short of oxygen. In view, therefore, of the high incidence of meconium staining in labour after the 40th week, many infants must suffer long periods of relative anoxia before delivery. Even if they ultimately survive, they may be damaged. For example, spastic diplegia is known to occur not uncommonly after such a syndrome where there has been no question of trauma at delivery.

Many clinicians have believed for a long time that "post-maturity" is potentially dangerous. I hope that this analysis and the oxygen findings will show that the problem is that of the failing oxygen supply in late pregnancy, a problem which is already present at the 40th week in a few cases, but becomes more important and more frequent the further pregnancy is prolonged. As pregnancy becomes prolonged after term, the "pregnancy process" begins to regress. The maternal weight drops, the maternal uterine blood flow lessens, the foetus becomes progressively short of oxygen, and its weight gain slows and may cease. In the extreme case pregnancy as a physiological process is over, but labour fails to occur and the foetus cannot escape death. This is the clinical history of an extreme case.

2751/48. This was a primigravida, aged 35, and with a menstrual cycle of 3-4/25-28. Pregnancy was normal, specialist antenatal care being given from the 8th week. The weight curve in the last few weeks is seen in Fig. 9. At the 44th week, the uterus was wrapped round the child, the foetal head was well into the maternal pelvis. On pelvic examination the cervix was thinned out over the head, the external os was high and in the sacral position, soft, and one finger could easily be inserted. Elective Caesarean section was performed under spinal anaesthesia. At operation no liquor was found, but the

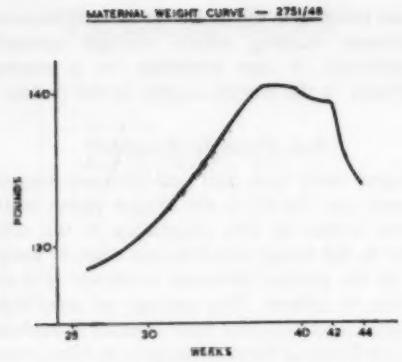

FIG. 9
Maternal weight curve—Case 2751/48.

child was covered with a thick layer of meconium. The foetal head, which was in the pelvis, was easily delivered. The maternal systolic blood pressure did not drop below 118 mm. of mercury. The child, a male, weighing 6 pounds 12 ounces, was limp. Indentation marks from pressure of the uterine wall were present on the child's body, and the skin was beginning to desquamate. The child was resuscitated with difficulty, gasped in 90 seconds, and did not breathe for 8 minutes. The child was transferred to the Special Nursery where it died in 15 hours, having had constant respiratory difficulty, with cyanosis even in oxygen. At postmortem examination meconium was found in the stomach. The lungs, which were aerated at the margins, were generally congested and solid. There was no other gross abnormality. Histology of the lung showed widespread inhalation of amniotic sac contents, and of the liver some central necrosis of lobules.

I agree that in this extreme form the syndrome is uncommon, but all prolonged pregnancies show lesser degrees of this picture.

How then can the clinician attack the problem of late pregnancy anoxia? In the present state of our knowledge it is impossible to select those cases in primigravidae likely to show a deficient oxygen supply to the foetus at the 40th or 41st weeks, partly because nearly 50 per cent of all pregnant women are delivered during those 14 days. There are, however, certain factors like pre-eclampsia or threatened abortion early in pregnancy which predispose to an early fall in the oxygen supply. Patients with these clinical abnormalities are better delivered at least by the end of the 40th week, and may with advantage be delivered a week or so earlier.

Clinically, however, the main problem is in primigravidae, and becomes important after the end of the 41st week. What then is the size of that problem?

Twenty-one per cent of all primigravidae are delivered after the end of the 41st week. In this 21 per cent are:

- 51 per cent of all unexplained deaths (mature).
- 83 per cent of all anoxic deaths in difficult labours.
- 40 per cent of all traumatic deaths in difficult labours.
- 43 per cent of all major difficult labours.
- 36 per cent of all Caesarean sections for difficult labour.

Have we got to take this whole 21 per cent into serious consideration, or is there any further guide to aid in selection of cases more likely to be affected than others?

The Influence of Maternal Age

Advancing maternal age should be considered as another clinical abnormality carrying additional hazards to the foetus. It is seen in Fig. 10 that the incidence of unexplained obstetric deaths rises with the age of the mother. In primigravidae the rise is greatest over the age of 30 and the rate is nearly 3 times as high in primigravidae over 30 as in those under that age. There is a similar rise with age in multigravidae. The obstetric death rate due to difficult labour also rises with age, the main rise taking place after the age of 25. It is interesting to note the fall in the obstetric death rate in this group in primigravidae over 35. For many years, Caesarean section has been used much more readily in the older primigravida undergoing difficult labour, and it is obvious that many babies have been saved. The rise in incidence of obstetric deaths due to difficult labour in association with rising maternal age reflects the greater incidence of difficult labour in older primigravidae (Baird, 1952a, b), and the lessened ability of the foetus of the older woman to stand even normal labour, as exemplified by death rates in the unexplained group. The increase of the death rate with age is independent of the duration of the pregnancy, and the older primi-

gravida is no more likely to go post-mature. If the mother is over 25, there is a much greater risk that her foetus will die of anoxia or will die because of difficult labour. The foetus is also much more likely to be called upon to face a difficult labour. All risks increase the longer pregnancy is prolonged. The problem of obtaining the first child alive is particularly important in the older primigravida in view of the greater value attached to the child by the older woman and a less likely chance of a family of reasonable size if the first child is stillborn.

Clinical Management of Difficult Labour

With the further clinical guidance given by a study of maternal age, I would suggest the following broad principles in management of labour to minimize the risk of death due directly or indirectly to anoxia.

Prevention of death from *birth trauma* is primarily a problem of obstetric skill at delivery, but is complicated after the 41st week by the falling oxygen supply to the foetus. A foetus, already anoxic and passing meconium, or already suffering local cerebral anoxia due to pressure, and manifesting this by slowing of its heart rate, may be killed by forceps delivery which a foetus, not already anoxic, would easily withstand. Careful assessment of the likely degree of difficulty should be made before delivery is begun, and especially in the older woman Caesarean section may be preferable.

Death due to *anoxia* in prolonged labour is usually preceded by a long period during which the liquor is stained with meconium. Frequently the membranes are intact, however, and meconium may not be visible. In cases of prolonged labour after the 41st week, it may help to tap the hindwaters. If the liquor is stained with meconium the foetus is already anoxic. The presence of meconium in the liquor indicates that the foetus has been short of oxygen, but unless it is becoming thicker or more yellow it does not, unfortunately, indicate whether the supply is deteriorating even further, or whether it is remaining just under distress levels. The foetal heart rate is not a good guide in such cases, as it frequently stops without any preceding period of slowing or irregularity. In the management of such cases it helps to consider the age of the mother. If she is over 30, it is probably best to perform Caesarean section for the sake of the child as soon as the presence of meconium is noted. In young primigravidae, dysfunction labour is uncommon and foetal distress is seen less often, but even here, if labour is unduly prolonged and there is passage of meconium, Caesarean section should be performed earlier

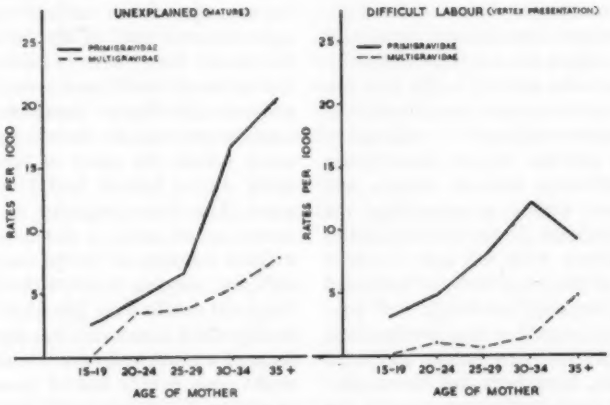

FIG. 10

Obstetric Death rates—the influence of parity and maternal age.

than the duration of labour itself, or the condition of the mother, might indicate. During the waiting period, oxygen should be given to the mother by B.L.B. mask, as this will almost certainly improve the oxygen supply to the foetus (Landais, 1892; Waters and Harris, 1931).

Anaesthesia. It is important to choose the safest anaesthetic for operative delivery of the already anoxic foetus. In the present state of our knowledge it appears that, for the foetus, spinal, local or caudal is best (Taylor *et al.*, 1951; Watts *et al.*, 1951; Batten, 1943). Any fall in maternal blood pressure which might occur can be controlled with Methidrine, and oxygen can be given to the mother until the child is delivered (Batten, 1943). During the induction period of most general anaesthetics, there is a time when the maternal oxygen supply is impaired (McClure *et al.*, 1939, 1948). If there should be difficulty in induction and maternal cyanosis should occur, the saturation of the mother's arterial blood drops only to some 80 per cent, but the oxygen tension drops by half, and very little oxygen would be transferred to the foetus during this time. Further, the infant born after the use of general anaesthesia may be handicapped by the presence of depressant anaesthetic gases in its own blood (Smith and Barker, 1942; Taylor *et al.*, 1951).

Resuscitation. I would like briefly to discuss the problem of resuscitation of the anoxic infant. Even though the rise in the obstetric death rate after term is due mainly to a rise in stillbirths, many of the babies who are lost in the first few days could be saved by expert resuscitation at birth. When operative delivery is undertaken because of foetal distress, expert resuscitation may make the difference between success and failure. The natural person to resuscitate the infant is the paediatrician (if specially trained in resuscitation methods), who will care for it in the first few days of life. Since 1948 we have had the benefit of an increased paediatric staff who have taken a special interest in this problem and in the last few years very few babies, delivered after the 40th week, have been lost neonatally. The techniques of resuscitation are outwith the scope of this discussion, but I would like to mention the importance of emptying the stomach of the infant who has been anoxic at birth. Anything up to 20 ml. of sticky meconium-stained mucus may be present and, if not removed, may well be inhaled during the respiratory difficulties of the first few days (Ahvenainen, 1953).

The Problem of Unexplained Deaths

In Table VII are seen the causes of obstetric death in primigravidae after the 41st week of gestation. It is taken from the 1939-51 series and demonstrates the risks of prolonged pregnancy where obstetric care has not been specially directed at the problem.

TABLE VII

Cause of Obstetric Death after the 41st week of Pregnancy in 10,758 Primigravidae

Cause		Per cent	
Difficult Labour (Vertex)	Anoxia ..	23·8	48·5
	Trauma	13·3	
Malpresentation: Cord		11·4	7·6
Deformity			
Unexplained (Mature)		32·4	43·9
Toxaemia		4·8	
Other		6·7	
Total			100·0 (105 cases)

It will be seen that the suggestions outlined for the management of difficult labour might save approximately half of the babies lost after the 41st week. Better care in labour, however, cannot influence death rates from the other causes, and especially those "unexplained". Of all those unexplained deaths shown here, 30 per cent occur before the onset of labour, 50 per cent occur during labour, and 20 per cent are neonatal. The large majority of the intrapartum deaths occur early in the first stage of labour without warning, or in the second stage without sufficient warning to allow the child to be saved. Neonatal deaths were preceded by a short period during which meconium was passed in the second stage of a short and easy labour. Rapid delivery might save a very few of those babies but the incidence of "unexplained" deaths could only be reduced to any degree if labour and delivery could be achieved at a period of gestation at

which the oxygen supply to the foetus is still good. If labour could be safely and successfully induced at this time, the number of deaths from anoxia due to prolonged labour would also, of course, greatly diminish without recourse to Caesarean section.

Induction of Labour

It has been suggested that induction of labour might fail to influence the obstetric death rate in prolonged pregnancy, or might, in fact, create new dangers (Solth and Müller, 1949). In our experience, surgical induction of labour by artificial rupture of the hindwaters seems to be a safe and easy procedure, and does not appear to predispose to prolonged labour. In view of this, the indications for induction have been widened in recent years, and, especially since the work of McKiddie in 1948-49, induction has been performed in many instances for post-maturity alone.

In Table VIII is seen the induction rate in primigravidae since 1948 according to the week in which delivery occurred. From 1948 to 1951 induction was performed for the more commonly accepted indications, for example, pre-eclampsia, but it will be noted that already we were beginning to induce labour more often after the 42nd week. In 1952, the induction rates doubled as indications were widened. In the early weeks, for example, milder cases of pre-eclampsia were induced, but in the 42nd and 43rd weeks many cases were being induced for "post-maturity". The results from the point of view of foetal mortality were very good (see Table IX). A study however, of the incidence of difficult labour suggested that the number of cases of major difficult labour was becoming less, and this seemed to be associated with the rising incidence of induction after the 40th week. It was decided, therefore, as a controlled clinical procedure, to increase the number of inductions after the 41st week, not only because of the likely influence on the obstetric death rate, but to see if cases induced at that time would have an easier and shorter labour.

In the Aberdeen population 21 per cent of primigravidae are delivered after the 41st week. It was obviously difficult to induce all cases. The obstetric death rates from unexplained causes and from difficult labour, and the incidence of difficult labour itself, are considerably less amongst younger women.

If the high risk group is defined as those cases who are aged 25 and over, and who go past the 41st week, it amounts to only 8 per cent of all primigravidae. It was therefore decided that all primigravidae over the age of 25 should be admitted to hospital and surgical induction performed if labour had not begun some 5 to 7 days after the estimated date of delivery, provided those dates seemed accurate and the infant was of reasonable size. Routine induction, therefore,

TABLE IX

Obstetric Death Rate after the end of the 41st week of Pregnancy in Primigravidae

Years	No. of Cases	Obstetric Deaths	Rate per 1,000
1948-49	400	14	35·0
1950-51	359	7	19·5
1952-June, 1953 ..	259	4	15·4
January to June, 1953	91	1	11·0

TABLE VIII

Incidence (per cent) Surgical Induction of Labour in Primigravidae

Week of Delivery ..	−37	38-39	40	41	42	43+	Uncertain	Total
1948-51	9·4	9·8	5·5	6·3	6·8	12·8	7·5	7·5
Total Cases	254	573	693	813	501	258	412	3 504
1952	13·5	10·0	14·7	9·7	10·4	28·3	20·0	14·0
Total Cases	52	130	150	216	115	53	144	860
January to June, 1953 ..	16·1	13·2	11·1	23·0	46·5	32·0	26·7	23·4
Total Cases	31	76	90	113	71	20	60	461

applied to only 8 per cent of our booked primigravidae. Artificial rupture of the hindwaters was performed in those cases without regard for the position or condition of the cervix, or the position or station of the head.

Results of Treatment

In Aberdeen Maternity Hospital

Over the last few years in booked primigravidae there has been a general improvement in results due to a better understanding of the problem, improved standards of care in labour, improved methods of resuscitation and, recently, following more frequent induction of labour. The figures shown for the first half of 1953 are based on a very small number of cases, but they are promising and the improvement has been progressive.

The obstetric death rate (Table IX) for deliveries after the 41st week fell by 15 per 1,000 total births soon after the importance of late pregnancy anoxia was first realized, and by another 10 per 1,000 during the period when the incidence of induction was increasing.

The effect on *major difficult labour* appears to confirm our impression that induction does not predispose to difficult labour, and that it may, in fact, prevent its occurrence (Table X). In the first half of 1953, the incidence of major difficult labour in deliveries after the 41st week was the same as the incidence in deliveries in the 40th week.

Table X

Major Difficult Labour after the end of the 41st week of Pregnancy

Years	Difficult Labour	Rate Per cent	Total Cases
1948-51	81	10·7	759
1952-June, 1953 ..	12	4·6	259
January to June, 1953	3	3·3	91

The incidence of *Caesarean section* has not fallen (Table XI). Recently Caesarean section for difficult labour has become less frequent, but the fall has been more than balanced by a rise in the number of Caesarean sections performed for foetal distress. Up to 1952 it is possible that a slight increase in the Caesarean section rate, due mainly to the indications of foetal distress and advancing maternal age, may have played the major part in lowering the death rates of postmature infants, but if the incidence of major difficult labour should persistently remain low as a consequence of more frequent induction of labour, the overall Caesarean section rate after the 41st week will remain at its present low level.

Table XI

Caesarean sections after the end of the 41st week of Pregnancy in Primigravidae

Years	Difficult Labour (per cent)	All Other Reasons (per cent)	Total Cases
1948-49	2·5	1·0	400
1950-51	3·0	1·4	359
1952-June, 1953 ..	2·3	2·7	259
January to June, 1953	—	3·3	91

When routine induction is performed, "foetal distress", manifest by heavy meconium staining of the liquor, may be found. Especially in the older primigravidae the decision is usually made to perform an elective Caesarean section in the interests of the child. The typical picture is seen in the following case.

Mrs. H., a primigravida, aged 37 years, had been married for 12 years. Routine antenatal care was undertaken from the 8th week of pregnancy by a senior consultant, and the pregnancy was clinically normal. There was a steady maternal weight gain till the 39th week of pregnancy, from which time the weight remained unchanged till the 41st week and there was a loss of 2 pounds by the 42nd week. Routine surgical induction of labour was performed at the beginning of the 42nd week, and 15 ounces of liquor, dark green and thick with meconium, were drained from the uterus. Elective lower segment Caesarean section was performed under spinal anaesthesia. The child, a female, weighing 8 pounds 2 ounces, was in good condition at birth, responded to routine resuscitation, and survived without incident.

The oxygen capacity of the foetal blood was high, being 24·6 vols. per cent. The saturation of the blood in the umbilical vein was 31 per cent, and of the blood in the artery 6 per cent. This foetus was already short of oxygen and had no reserve to allow it to withstand labour without serious and probably fatal anoxia.

In Aberdeen City

A very high standard of work and careful management of each case is necessary to obtain

the best results. Evidence of the effect of improving standards of obstetric care is seen in Fig. 11 which illustrates the trends in the stillbirth rate in the City of Aberdeen for the years from 1939 to 1952. Each stillbirth has been studied and a clinical cause assigned to the death.

The situation in Aberdeen is favourable for such a clinical investigation as, in recent years, about 95 per cent of primigravidae and 70 per cent of multigravidae are booked for confinement under the care of specialists in hospital. Booked cases attend the antenatal clinic, and each clinic is conducted under the supervision of a consultant obstetrician, so that the standard of observation and of recording is uniformly high. A very good liaison exists with domiciliary midwives and general practitioners, so that cases under their care are referred quickly if abnormalities develop, and full and accurate information is available if a stillbirth should occur, so that the causes of death in domiciliary cases can also be accurately assessed. A fall of 50 per cent has occurred in the stillbirth rate from about 40 per 1,000 before the war to 20 in the last few years. The interplay of the many factors responsible for this has been discussed elsewhere (Baird *et al.*, 1953; Baird and Walker, 1954), but I wish to concentrate on deaths of mature infants from birth trauma (of all forms) and "unexplained" causes. For the sake of simplicity the rates for both causes are combined in a single line in the diagram since they run parallel and close to each other.

The fall in the period 1939 to 1945 was due probably to the increasing proportion of cases confined in hospital, as a result of expansion of accommodation. The rise in 1946 to 1948 occurred mainly because of a great increase in the birth rate affecting first, second and third births, and due to an accumulation of war-postponed pregnancies. The patients were, therefore, older and in addition many more were confined in their own homes. As the stillbirth rate in both cause groups rises with maternal age, and as the emergencies of labour cannot be dealt with as quickly, and as effectively, under domiciliary conditions, a rise in the rate in that period is only to be expected. The fall since 1949 is due to the fact that nearly all primigravidae are confined in hospital (the falling birth rate made this possible) and to the new methods of management described. Deaths from birth trauma at all stages of gestation have become uncommon; in 1952, for example, there were no

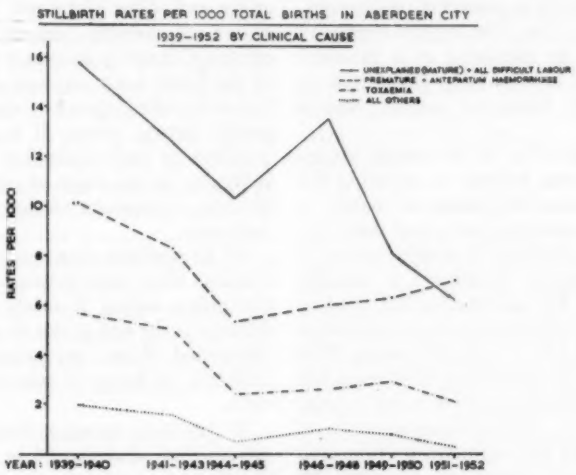

FIG. 11

Stillbirth Rates per 1,000 total births in Aberdeen City, 1939-1952 by clinical cause of stillbirth.

obstetric deaths from birth trauma in deliveries of 1,000 booked primigravidae. The improvement in "unexplained deaths" is due almost exclusively to the elimination of stillbirths after the 40th week of gestation. Further fall in the stillbirth rate is likely to be slow, as other causes are not so amenable to surgical skill, and there is convincing evidence that they are related to biological and environmental factors, the removal of which would be difficult and slow.

Discussion

Since the end of the war, comprehensive research has been conducted in Aberdeen into the causes and prevention of stillbirth and early neonatal death. My own particular interest, since joining the staff of the University Department in January, 1948, has been to study causes of death in babies delivered just before, at, or after term. Of special interest were those cases where anoxia was responsible for death of a foetus fully grown and otherwise normal.

In this paper I have stressed the importance of a falling oxygen supply as pregnancy becomes prolonged as a causal factor in many of those deaths. Quantitative estimations of oxygen lend support to those who, on clinical grounds, have held that post-maturity is potentially dangerous. Unfortunately, of course, the oxygen supply to the foetus cannot be measured as a practical guide to treatment in individual cases, and so treatment must be based on careful clinical assessment.

I have mentioned a few of the clinical guides that have been found helpful in planning the conduct of each case. The maternal weight is taken routinely at antenatal visits, and there are, of course, many variations of weight curves in individual pregnancies. However, a steadily rising curve with a halt and then a fall of some pounds at or after term is probably a significant sign in the type of case we are discussing. This valuable sign may be masked by fluid retention due to mild pre-eclampsia which is, of course, common at this time. Gradual disappearance of the liquor amnii and the picture of a firmer and more easily palpable foetus, as described by Wrigley (1946) and Mills (1953), does occur. Adequate liquor does not, however, preclude a dangerous degree of anoxia, as exemplified by the second case history.

As a result of our experience in the last few years, we have formulated certain general principles of management which we think are a great help when used in conjunction with a careful clinical assessment of each case.

(1) Induce labour before 40 weeks in cases of pre-eclampsia, or in those in which bleeding has occurred in the early months of pregnancy.

(2) Primigravidae under 25 with otherwise normal pregnancies are allowed to go into labour spontaneously, but induction is performed if, after term, maternal weight is falling steadily, the liquor appears to be lessening, or pre-eclampsia develops.

(3) If foetal distress develops during labour and especially if meconium is present in the liquor, oxygen is given to the mother and the case assessed on clinical grounds. Especially in the older primigravida, and if a further period of prolonged labour is to be expected, Caesarean section is seriously considered on the indication of "foetal distress". With the already anoxic foetus, Caesarean section is often preferred if forceps delivery would be difficult and might put an undue strain on the foetus.

(4) In primigravidae over 25 labour is induced at the end of the 41st week. If, at induction, the liquor is heavily stained with meconium, elective Caesarean section is performed. Slowing of the foetal heart may not occur, or occurs too late to be relied upon as a sign of uncomplicated anoxic anoxia alone. It is unusual in primigravidae to find meconium staining at routine induction at this stage of pregnancy, and so, in practice, Caesarean section will not often be necessary.

(5) In multigravidae somewhat similar action is taken. Since most labours are short and easy, Caesarean section is rarely called for, but induction at the end of the 41st week is frequently performed. Where the previous child has been stillborn, delivery is usually achieved before term.

It may seem to some disappointing and surprising that what should be a natural and easy function requires so much care if the best results are to be obtained. There are several reasons for this.

Firstly, in modern society there is no natural selection of women most efficient in reproduction and the higher the standard of obstetrics the less the selection.

Secondly, as stressed by Baird (1952a, b), and Baird and Illsley (1953), youth and optimal health are necessary for easy and safe childbearing, and of special importance in this paper is the demonstration that the incidence of "unexplained death" of the mature foetus and of death directly due to difficult labour are lowest in the age group 15 to 19 and increase steadily with increasing age.

The liability to post-maturity is just as great in primigravidae under 20 as in any other age group, so that, if post-maturity is regarded as "abnormal", then the young woman is no more efficient than older women in this respect. Nevertheless the consequences for the child are very much less serious in the younger woman, partly because of a much lower incidence of difficult labour. A study of foetal distress rates shows, however, that in the young woman oxygen supply to the foetus does not deteriorate so quickly, suggesting that the uterine blood flow is more efficient, and that there is a greater reserve.

I have shown that, as pregnancy is prolonged beyond 40 weeks, the foetus suffers from an increasing shortage of oxygen, and under certain conditions this can prove fatal. It is not at all clear why this deterioration should occur. There is still a great deal to be learned about the physiology of normal pregnancy and the effects and mechanism of deviations from the normal. It would appear that, in most women, prolonged pregnancy is pathological, but it is impossible to say why labour should fail to occur or when, in the given case, a delayed onset of labour becomes particularly dangerous to the foetus.

Meantime, therefore, we must attempt to assess the dangers to the foetus in the given case, and base treatment on all the information at our disposal without, if possible, increasing the risks to the mother.

Our experience of induction of labour and indications for Caesarean section have been very briefly described. The results are encouraging, but a longer time will be necessary before the role of induction of labour can be more clearly defined and the risks of the procedure properly evaluated. In our experience, induction as performed on the indications discussed appears to lessen the risks to the foetus without increasing the risk to the mother.

Note

The tables from which Figs. 4, 5, 6, 7, 8, and 10 were constructed have been omitted at the request of the editor.

In Fig. 4 the rise in the obstetric death and stillbirth rates from the 41st to the 43rd week is significant, $P.<\cdot01$. The rise in the neonatal death rate is not significant. In Fig. 5 the rise in the rate of "unexplained mature" deaths from 41st to 43rd weeks in primigravidae is significant, $P.<\cdot05$. The rise in the "difficult vertex" rate just fails to reach the 5 per cent level of significance on the one tail test. The increases in "unexplained mature" and "difficult vertex" rates after term in multigravidae because of small numbers are not statistically significant.

In Fig. 6 the difference between rates at 40 and 43 weeks is highly significant in each graph. In Fig. 7 the difference between rates of "cause unknown" at 40 and 43 weeks is highly significant, and rates for prolonged labour plus pressure on the head are significant, $P.<\cdot001$.

In Fig. 8 both graphs are highly significant.

In Fig. 10 rates for primigravidae are significantly greater at the 30-34 age group than at the 20-24 age group. At the same age groups in multigravidae the differences are not statistically significant.

Acknowledgments

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THE MANAGEMENT OF INFERTILITY*

BY

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INTRODUCTION

THE management of infertility has, during the last 30 years, gradually assumed an important place in medical practice. It has undoubtedly increased our knowledge of sex physiology. It has not been without its rewards, material and otherwise, to the profession. But has it been of direct benefit to our patients either individually or as a group? If so, what is the extent of the benefit and how has it been conferred? How should cases of infertility be managed and in what directions do present-day methods of investigation and treatment require modification? These and similar questions are relevant to the review of a subject which appears to be obscured by clouds of fantasy, wishful thinking, false premise, and quack remedy, as much today as it was in the days of love potions and fertility amulets.

RESULTS OF TREATING INFERTILITY

Any consideration of individual methods of investigation and treatment is best approached against a background of the results which may be expected. A few years ago Mr. Bender followed up 700 consecutive cases of *primary* sterility seen by me or in our clinic 3 to 17 years previously (Bender, 1952). The number of women traced represented approximately 90 per cent of those seen. Every woman was required to have had 2 years real opportunity for conception and of these all were included in the analysis—no matter whether they were investigated and treated or not, no matter whether some lesion was found which necessitated hysterectomy or other radical procedure, no matter how sterile their husbands or how closed their tubes. The longer the period of follow-up the greater the number found to have become pregnant. More than 46 per cent of the women had in fact conceived, and it could be calculated that if all had been followed up until the menopause not less than 50 per cent would have had at least one pregnancy.

Considering the material, and compared with published figures, this is a high success rate. How was it obtained?

Hormone therapy was only used when there was gross menstrual upset such as amenorrhoea, and never for supposed uterine hypoplasia and hypothetical recurrent early abortion. No attention was paid to the possibility of cervical hostility, although in a few of the early cases precoital douches were advised when all else failed. Artificial insemination with husband's semen was used rarely, and then with a clear indication such as impotence in the male or absence of the vaginal cervix in the female. A.I.D. was never employed. Empirical remedies such as vitamin E, diet, antispasmodics, antibiotics and the like, were shunned. The daily recording of temperature was hardly ever instituted, and then only as a last resort, or when the menstrual cycle was grossly irregular. Special operations such as myomectomy, salpingostomy, salpingolysis, ventrosuspension and epididymo-vasostomy were carried out in carefully selected circumstances. In the vast majority of cases, however, nothing was done except dilatation of the cervix, curettage and one or other tubal patency test; and nothing was given except advice.

Moreover, judging by the time at which conception occurred in relation to treatment, there is good reason to believe that in not less than

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50 per cent cases, and probably in 60 per cent, the pregnancy resulted by chance and was entirely unrelated to any treatment given. In the remainder, treatment may have played a part but here the operative word is *may*, for Sharman (1952) points out that the pregnancy rate during the first 3 months following insufflation, or following hormone therapy, is exactly the same as that which follows bimanual examination alone. Indeed, evidence fast accumulates to show that, except perhaps for putting the patient in a frame of mind conducive to conception, the more usual forms of treatment have little effect.

That the occurrence of pregnancy after treatment does not imply that fertility has necessarily been raised is further shown by the fact that many couples find it impossible to repeat the performance. In the series under review two-thirds of the women who had conceived by the time of follow-up had done so only once, and most of these continued to be infertile afterwards.

Management

Considerations such as the above, study of the literature and personal experience lead next to the suggestion that, as yet, there are only 4 basic investigations which are of any real *practical* value in the management of infertile marriage.

(a) *Clinical history and examination of both partners*

This obvious approach needs no elaboration but it is surprising how often it is performed so perfunctorily as to be of little value. Under this heading should be emphasized the need to exclude coital problems—failure to penetrate, infrequent coitus, coitus at the wrong time, and above all male impotence which is more common than is generally realized.

(b) *Semen analysis*

Examination of semen obtained from the vagina after coitus is inadequate and can be misleading. But even given a full masturbation specimen the interpretation of the findings can be extremely difficult, for there is no agreement on the significance and relative importance of features such as volume of fluid, sperm density, total count, motility and morphology. All must obviously be considered together, but under conditions of day to day practice sperm density appears to be the most valuable single guide and motility the least significant. The need for care in interpretation, however, is illustrated by the fact that in the series of cases already mentioned 33 per cent of men not azoöspermic but with a count of less than 10 million per c.cm. were ultimately responsible for a pregnancy, while the figure was only between 50 and 60 per cent amongst the men with a count of more than 60 million per c.cm. These findings are based on not less than 2 examinations of semen, the higher count being recorded here. Spontaneous variations were also excluded as far as possible by examining the semen again as soon as the wife of a grossly subfertile man conceived. There were 2 cases in which a man produced seminal fluid containing no spermatozoa on more than one occasion and yet still subsequently found himself a father.

Poor quality semen is not so serious a matter as is sometimes suggested; it may delay conception but nevertheless a pregnancy will occur sooner or later in a large proportion of cases. Here, again, is a background against which must be weighed any claims for the successful treatment of male infertility by thyroid, testosterone, gonadotrophin, vitamin E and by A.I.H.

Testicular biopsy has a limited place except for research purposes. It is nevertheless useful in a few cases in which there is good reason to suspect an obstructive lesion in the vas and epididymis which may be amenable to plastic surgery.

(c) *Tubal patency tests*

It is generally recognized that tubal patency tests can give false or misleading results, but the extent of their fallibility is often not realized. It is here illustrated by study of 1,023 consecutive tests carried out on 428 private patients and 478 hospital patients, the details having been published elsewhere (Jeffcoate, 1953). The hospital cases were all dealt with during the 4 years 1949-1952, so that the period of follow-up is short, and further observation may bring to light even more discrepancies. Insufflation was always carried out under general anaesthesia while hysterosalpingography was, as a rule, performed on the unanaesthetized patient who

had previously been given pethidine and nitroglycerine. The behaviour of the opaque medium was studied by screening and by photography.

The Reliability of Tubal Patency Tests

Type of Test	Proved False *Negative* Rate Per cent	Proved False *Positive* Rate Per cent
Insufflation only ..	37·0 (in 116 cases)	3·2 (in 369 cases)
Salpingography only	15·1 (in 86 cases)	0·8 (in 380 cases)
Both Tests agreeing	15·1 (in 32 cases)	Nil (in 35 cases)

The two tests gave different results in 30 per cent (in 116 cases).

Despite the fact that the insufflation test was always tried not less than 3 times, a negative finding was proved by hysterosalpingography or by pregnancy to be fallacious in 37 per cent cases. A positive result was found (by laparotomy or by hysterosalpingography) to be fallacious or misleading in 8·6 per cent cases. In 3·2 per cent it was erroneous in that the tubes were found to be closed and converted into hydrosalpinges; in the remainder it was misleading in so far that, although at least one tube may have been open, both were affected by peritubal adhesions.

Evidence of bilateral tubal occlusion on salpingography was proved (by pregnancy or by laparotomy) to be fallacious in 15·1 per cent cases, but findings leading to the conclusion that the tubes were normal only proved incorrect in less than 1·0 per cent cases. There was another group of 72 cases in which salpingography suggested the presence of peritubal adhesions and in only 1 of these is it known that the diagnosis was incorrect. However, the matter was only put to the test of laparotomy in 11 cases. In order to diagnose peritubal adhesions, it is essential to use a medium which is not quickly absorbed because its spread within the pelvis may need to be studied over the course of a week or longer. For this reason the use of aqueous radio-opaque preparations deprives hysterosalpingography of one of its most important applications.

When both insufflation and hysterosalpingography were carried out on the same patient with similar results, errors were less frequent, especially if the findings were normal. However, in at least 5 of the 32 cases in which both tests gave evidence of bilateral tubal occlusion, the findings were incorrect.

Many nowadays use some form of kymograph to test tubal patency and some go so far as to say that study of the type of tracing obtained makes it possible not only to determine tubal patency but to diagnose tubal hypoplasia, peritubal adhesions, and even tuberculosis, by the type of tracing obtained. This presupposes first that the oscillations are produced by tubal contractions and there is now a good deal of evidence to show that this is incorrect. Indeed, anyone who cares to carry out the test while the tubes are under observation at laparotomy will soon doubt this view. Moreover, such experiment will quickly reveal how the type of tracing bears no relation to the state of the tubes.

Apart from their limited usefulness these complicated machines introduce many difficulties —not the least of these being the surreptitious escape of gas from one of the many joints they contain. The old-fashioned simple machine is more reliable and has much to be said for it.

The recognition of cornual spasm during patency tests has led to the suggestion that such spasm can cause sterility which can be successfully treated by giving antispasmodics during the fertile period. The observation that some women conceive during such treatment is said to justify this claim. In fact, however, as our findings show, the spasm occurring during insufflation is often not relieved even by general anaesthesia let alone by less potent drugs and, moreover, at least 60 per cent of women who show spasm enough to give a false negative insufflation test will conceive subsequently without any treatment at all!

(d) *Histological and bacteriological examination on the endometrium*

This fourth line of investigation should be carried out under anaesthesia. It is important from the standpoint of estimating ovarian function and excluding genital tuberculosis. It also allows an assessment of uterine development. In fact, however, there is no firm evidence to show that uterine hypoplasia *per se* causes

infertility. Moreover, if it is present and is the result of ovarian hypofunction, it is the absence of ovulation associated with the latter which requires treatment. If, on the other hand, hypoplasia occurs despite adequate ovarian function, then no amount of hormone therapy will influence it. The administration of oestrogens and progesterone for supposed hypoplasia or for hypothetical recurrent early abortion is without sound foundation, and has never been proved to have any value so far as the treatment of infertility is concerned.

If the above four lines of investigation are carried out meticulously and the results analyzed with care, a possible cause for infertility will be found in a large number of cases. Those in which one is not found fall into two groups:

(*a*) Those in which pregnancy occurs soon after the investigation and in which it is possible that dilatation of the cervix, tubal insufflation or even vaginal examination, may have eliminated some form of cervical "hostility" or other physical or mental bar to conception.

(*b*) Those in which sterility persists but in which an obvious cause will ultimately be found providing they are followed up—if need be to postmortem examination. The sort of lesion which may be missed is peritubal adhesions which can be as real a mechanical obstruction to the ovum as is tubal occlusion itself (Bender, 1949). Moreover, it is more important to find this cause because it is often amenable to surgical treatment whereas tubal occlusion is not. In my experience, salpingolysis in such cases is frequently successful whereas, so far, and despite using various techniques, I have not yet had a single case in which a true salpingostomy has resulted in pregnancy.

Other Investigations and Treatment

Two other procedures which have obtained a measure of popularity deserve comment:

1. *Determination of the occurrence and time of ovulation*

Absent or infrequent ovulation is nearly always indicated by the menstrual history. In women of reproductive age and menstruating regularly, anovular cycles are occasional rather than regular occurrences. Indeed it is probably fair to say that not more than 4 per cent cases of prolonged infertility amongst menstruating women are due to failure of the ovary to ovulate; and this may well be a high estimate. Anovulation is certainly not the first cause to look for, and painstaking daily recording of the temperature ought not to be the first line of investigation. It may be useful for a few months when the menstrual cycle is unusual and there is need to determine the fertile period; it may be carried out as a last resort when no other infertility factor can be found and the woman remains childless. Many women, however, and surprisingly their medical attendants too, seem to think that keeping a temperature chart will help them to conceive. On the contrary it is a daily reminder of their complaint, it changes marital love into a mathematical exercise and may well hinder rather than encourage conception. Even if the menstrual cycles are proved to be regularly anovular there is no form of hormone or other therapy which can be prescribed with confidence in its success.

2. *Postcoital and cervical mucus invasion tests*

These are interesting academic pursuits, and are satisfying to the uncritical observer in that the scope of their interpretation is so wide as to make it possible to find a cause for infertility in every case and to provide a "reason" for instituting treatment with diet, antibiotics, local remedies, hormones, or whatever is in fashion. From the *practical* standpoint the present situation in regard to such tests can be summarized by saying that those who never carry them out and never attempt to treat "cervical hostility" other than that manifested by some gross abnormality of the cervix, can show as good results among their patients as can those who pay attention to these matters.

The receptivity of the cervix for spermatozoa remains a subject eminently suitable for research but it need not yet concern those whose interests are confined to routine practice.

The Disadvantages of Investigating and Treating Infertility

The investigation and treatment of infertility is not only of limited value; it can be harmful.

An acute exacerbation of previously existing chronic infection follows 1 per cent of tubal patency tests. Gross intravasation can be demonstrated by screening if not by filming in not less than 1 per cent cases submitted to hysterosalpingography. A pregnancy already present and unrecognized may be disturbed. Within recent years there have been 11 known cases in our clinic in which some form of tubal patency test, and often endometrial biopsy as well, was carried out when the woman was already pregnant—and this despite reasonable precautions being taken. None of these pregnancies came to harm but we only know of them because they did not do so. There may have been further cases in which early abortion took place.

The chief risk of dealing with infertility, however, is that it may react badly on the partners of the marriage. It is better to live in hope than to know the worst, so it seems wise never to tell any individual or couple that they are sterile—even if one could be sure that they are. Moreover, nothing should be said which will enable one partner to blame the other; wherever possible, infertility factors should be distributed between them. It should be recognized too that in all cases there is an optimum time at which to halt all diagnostic and therapeutic measures, and to persuade the patients to direct their attention to other matters. Otherwise, a complaint is turned into an obsession.

Conclusion

While it is true that in isolated cases the correction of some obvious abnormality in structure or function is dramatically successful, the evidence so far available goes to show that the handling of cases of infertility is of limited value except from the standpoint of prognosis. And even that can be woefully inaccurate. Nevertheless, it would be wrong to underestimate the importance of the comfort of mind which the investigation and treatment of their problem brings to those who are childless. Even if nothing comes of it, the infertile couple have the satisfaction in later years of being able to look back and feel that they at least took all humanly possible steps to remedy the matter. Fortunately, or unfortunately, they do not realize that the remedy is, as yet, rarely within the bounds of human knowledge and skill. So it is not surprising that those who ultimately achieve a pregnancy usually fail to "render . . . unto Caesar that which is Caesar's", and credit is given where no credit is due. In receiving it, however, let us not deceive ourselves.

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HISTIDINE EXCRETION IN NORMAL AND ABNORMAL PREGNANCY

BY

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THE clinical interest in the estimation of histidine in urine arose as a result of the observation of Voge (1929) that this amino acid, while absent from normal urine, is excreted in relatively large amounts during pregnancy. Voge suggested that estimation of histidine in urine may serve as a chemical test for pregnancy. This suggestion has been strongly supported mainly by Kapeller-Adler and her co-workers (Kapeller-Adler, 1933, 1936; Kapeller-Adler and Hermann, 1934, 1936; Kapeller-Adler and Hass, 1935; Kapeller-Adler and Schiller, 1935). These authors claim that the urine of men and non-pregnant women is, except occasionally, free of histidine, that histidinuria begins soon after the embedding of the ovum, persists throughout normal pregnancy and that it ceases only after parturition or after the expulsion of the dead ovum (Kapeller-Adler, 1950).

An important development followed when Kapeller-Adler (1941a, 1941b, 1949, 1950) announced that in eclampsia or severe pre-eclamptic toxaemia the histidine test becomes negative and that in these conditions histamine is being excreted instead of histidine. According to this author histamine is absent from the urine of normal pregnant and non-pregnant women. Kapeller-Adler suggests that under normal conditions histidine is destroyed in the liver by the enzyme histidase, that in pregnancy the histidase is inactivated by the chorionic hormones allowing histidine to escape in the urine and that in eclampsia the histidine is converted to histamine. Thus, according to Kapeller-Adler, disappearance of histidine and appearance of histamine in the urine during pregnancy is a prognostic sign of extreme gravity.

No conclusive evidence in favour of this hypothesis has been provided and no general agreement has yet been reached upon the value which can be attached to the estimation of histamine and of histidine in urine. Anrep *et al.* (1944) found that histamine is a normal constituent of urine. Gabrawy, Anrep and Barsoum (1950) reported that histamine excretion is not changed in normal pregnancy and that in eclampsia it is not increased. As regards histidine, Dodds (1930) denied that its excretion is related to pregnancy. Fox (1933) frequently found the test to be negative during pregnancy while Neuweiler and Grimm (1940) found it positive in many non-pregnant women. Langley (1941) showed that histidine is present in most urines and that there is no absolute increase in its excretion during pregnancy. Racker (1940, 1941) found histidine in the urine of males and of non-pregnant women while Page (1946), using Kapeller-Adler's method, reported as many as 30 per cent false negatives and 24 per cent false positives. Chattaway (1947) believes that the histidine test has no value unless applied to a single individual before and during pregnancy. On the other hand Pagliari (1950) was able to confirm most of Kapeller-Adler's observations upon the effect of pregnancy and of eclamptic toxaemia.

METHODS

All colorimetric methods of histidine determination are based on Knoop's observation (1908) that bromination of histidine gives a coloured compound. Since then almost every investigator has introduced some modification in the original method. In the latest and the most generally used modification by Kapeller-Adler (1949) 5 ml. of urine are mixed with an acidulated bromine reagent; after standing the excess

of bromine is removed by phenol and an ammonia reagent is added. On heating the mixture acquires a typical reddish-violet coloration which is matched in a photo-electric colorimeter against similarly treated standard solutions of histidine in water.

In the present research each step of this method was first subjected to a thorough control. Although satisfactory for quantitative estimations of histidine solutions in water the method was not found to be accurate when applied to urine. Histidine added to urine could be recovered only from urines of low specific gravity. With most urine samples the recovery was not complete and many urines gave negative results although histidine had been added. When different amounts of urine were used for the test the estimations were frequently higher with small amounts (1 to 2 ml.) than with the larger amounts (5 ml.). The least accurate were the estimations made on urine of high specific gravity.

The errors of the method were traced to four causes: (1) insufficient acidification of the urine before the addition of bromine; (2) insufficient amount of bromine in relation to the volume of urine used for the test; (3) interference of urinary pigments by their effect on the optical density of the sample and (4) presence of albumen in pathological urines. Some of these sources of error have been already recognized by Racker (1940), by Langley (1941) and by Page (1946). In order to eliminate them Kapeller-Adler's method was modified as follows.

The volume of urine used for the reaction was reduced. Instead of a single sample of 5 ml., two urine samples, one of 2 ml. and one of 1 ml., were run simultaneously each serving as a check for the other. Before bromination the urine was acidified, as suggested by Page (1946), by addition of 2 ml. of normal HCl. The bromine concentration was increased and the albumen, when present, was removed before the addition of any of the reagents. Instead of water, formalinized urine together with all the necessary reagents was used in the photo-electric colorimeter as a blank. Addition of formalin does not change the optical density of the solution but effectively prevents the histidine colour reaction. In this manner the interfering action of urinary pigments could be eliminated.

Reagents. (1) Normal solution of HCl; (2) the bromine reagent: 7·5 ml. of bromine in 500 ml. of glacial acetic acid and one litre of water; (3) 10 vol. per cent of liquified phenol in water; (4) the ammonia reagent: 400 ml. of ammonia (sp. gr. 0·88) added to 200 ml. of 10 per cent solution of ammonium carbonate in water; (5) formalin (40 per cent formaldehyde).

Procedure. (1) Measure volume and specific gravity of the urine; if albumen present boil after acidification with acetic acid and centrifuge.

(2) Label four tubes A, A′, B and B′. Place 1 ml. of urine in A and A′ and 2 ml. in B and B′. Add 0·2-0·3 ml. of formalin to A′ and to B′. Complete volume in the four tubes to 5 ml. with distilled water.

(3) Add 2 ml. of N.HCl and 2 ml. of the bromine reagent to each tube and allow to stand for not less than 10 minutes.

(4) Add 0·2 ml. of the phenol reagent to each tube to decolorize the excess of bromine and finally 0·8 ml. of the ammonia reagent. If turbidity appears after the addition of phenol the amount of the bromine reagent should be reduced.

(5) Heat the four tubes in a water bath to about 80° C. (one minute is usually sufficient); cool to room temperature and adjust volume to 10 ml.

(6) Using a photo-electric colorimeter and a blue filter determine the difference in density of samples A and B and their respective blanks A′ and B′.

The histidine concentration as calculated from the readings of the two pairs of tubes should not differ by more than 5 per cent. Within the range of 2 to 150 mg. per cent the density difference between the brominized urine sample and its formalinized blank is directly proportional to the amount of histidine present. Examples of histidine determination in urine and of quantitative recovery of added histidine by the original and by the modified method are given in Table I.

While very small amounts of bromine are required for quantitative estimations of histidine solutions in water, similar solutions in urine require much larger amounts. In order to

TABLE I

A. Histidine determination in urine by the original method and by its modification. All histidine concentrations are given in mg. per cent as monochloride.

Urine Sample	Amount of Urine used in ml.	Histidine Concentration in mg. per cent	
		By original method	By modified method
1. Male; sp. gr. 1010	1	20	26
	2	12	26
	5	traces	26
2. Male; sp. gr. 1030	1	15	107
	2	traces	104
	5	negative	80
3. Female, non-pregnant; sp. gr. 1018	2	30	57
	5	12	54
4. Female, pregnant in 6th month; sp. gr. 1016 ..	2	27	44
	5	20	41

B. Recovery of histidine added to urine by the original method and by its modification.

Subject	Histidine Concentration in Urine in mg. per cent		Histidine added to Urine in mg. per cent	Total Histidine expected in mg. per cent		Total Histidine determined in mg. per cent	
	Original method	Modified method		Original method	Modified method	Original method	Modified method
1. Male	negative	20	80	80	100	35	97
2. Male	negative	26	30	30	56	10	58
3. Female	negative	22	40	40	62	18	62
4. Female	7	52	40	47	92	27	94
5. Pregnant 7 months ..	20	30	40	60	70	51	72
6. Pregnant 6 months ..	22	48	40	62	88	52	86

brominize the entire histidine present in the urine bromine must be added in considerable excess. If, as done in several methods, the bromine reagent is added drop by drop so as to maintain only a "faint excess" of bromine the reaction is usually incomplete. It is obvious that many urine samples contain substances interfering with the bromination of histidine. In some samples even after addition of histidine a negative reaction may be obtained unless the concentration of bromine is increased.

RESULTS

The subjects under investigation were divided in three groups. The first consisted of 52 men, mostly laboratory attendants and members of the staff. The second group was composed of 42 non-pregnant women, mostly nurses and wives of the members of the first group. In the third group were 52 cases of normal pregnancy, all in the second half of gestation. Some of these were selected from the outpatients' department and kept in the hospital for observation; the rest were private cases. The ages of the subjects were between 18 and 47 years; none suffered from any abnormality or disease. Except for the subjects kept in hospital the usual routine of their life was not changed. At this stage of the investigation the diet was not controlled but notes were made describing the type and quantity of food consumed on the day before and on the day during the collection of urine. The urine was collected in 24-hour samples over chloroform and the determinations were made on the same day. Each period of collection began at 8 a.m.

In a total of over 600 estimations not a single urine sample was found to be free of histidine. This alone is sufficient to show that qualitative

determinations of histidine in random samples of urine can never be used as a pregnancy test. As regards the concentration of histidine in different urines and the amount excreted in 24 hours the variations were considerable but not related to any one of the three groups of subjects (Table II). In individual subjects whose histidine excretion had been followed for several days in succession the variations were less conspicuous so long as their diet was not greatly altered.

The effect of protein diet on the excretion of histidine. It had been first noticed by Kapeller-Adler and Schiller (1935) that administration of protein during pregnancy was followed by an increased elimination of histidine. No such effect could be observed, according to these authors, in men or non-pregnant women. On the other hand, Page (1946) found that oral administration of histidine to any subject increased its excretion in the urine, the effect being, however, more conspicuous during pregnancy. Most of this increase occurred within 6 hours after the administration.

In the present investigation 4 subjects from each group were kept for one day on a meatless and protein-poor diet which was changed, on the next day, to a protein-rich diet containing about 350 g. of meat. The respective means of the daily histidine excretions on the protein-poor diet were 336 mg. for men, 320 mg. for non-pregnant women and 382 mg. for pregnant women. On the protein-rich diet they were 529, 588 and 614 mg. respectively. In agreement with Page, the effect of protein administration was observed in all subjects independently of the group to which they belonged. In contradiction to Page, no significant difference could be detected between the three groups. The increase in the elimination of histidine was of the same order in pregnant and non-pregnant women.

On keeping some of the subjects on a protein-poor diet for several days, their histidine excretion was found to diminish abruptly on the first day and then more gradually until a minimum was reached in 3 to 4 days. On returning to a protein-rich diet the picture was reversed, the excretion was abruptly increased on the first day and reached a maximum a few days later. Again, no significant difference could be observed, in this respect, between pregnant and non-pregnant cases.

Histidine excretion in eclamptic conditions. According to Kapeller-Adler the histidine test may become negative in severe pre-eclamptic toxaemia or eclampsia, but not in other hypertensive disorders. The present investigation was made on 8 cases of typical eclampsia. Using the technique described in the present paper every urine sample of these patients was found to give a positive test for histidine. Furthermore, the histidine concentration in the urine and the total amount excreted per day were not significantly different from those of normal individuals kept on a protein-poor diet. It must be remembered, in this respect, that in pregnancy toxaemia meat is usually excluded from the diet and the total intake of food diminished.

The results obtained in 2 cases are given in detail in Table III. They were selected to show that the excretion of histidine, even in this grave condition, is greatly influenced by the character of the diet. In the first case in which meat was allowed the excretion was considerably greater than in the second in which the protein intake had been restricted.

The other 6 cases presented the same picture. Kept on a protein-poor diet, the average daily histidine excretion in 5 cases was 234, 286, 240, 385 and 270 mg. respectively with a histidine concentration in the urine varying between 18

TABLE II

Excretion of histidine by men and by pregnant and non-pregnant women in mg. of monochloride

Subjects	Number of subjects	Number of samples analyzed	Mean of concentration in mg. per cent	Lowest and highest excretion in 24 hours	Mean of excretion in 24 hours	St. div. of the mean
Men	52	190	40	200—676	421	±25
Non-pregnant women	42	196	38	192—612	380	±21
Pregnant women ..	52	226	50	204—794	460	±32

TABLE III
Histidine Excretion in Eclampsia

A. Severe pre-eclamptic toxaemia; B.P. 180/110; albuminuria++; pregnant 30 weeks. Food intake is not restricted and meat is allowed. The histidine test by the original method was in every sample consistently negative.

Days	Volume of Urine in 24 hours in ml.	Histidine Concentration in mg. per cent	Histidine Excretion in 24 hours in mg.
1	345	160	552
2	520	107	556
3	505	131	662
	Average	133	590

B. Eclampsia; B.P. 190/120; albuminuria++; several fits while in the hospital; pregnant 24 weeks. Strictly meatless diet. The histidine test by the original method was in every sample consistently negative.

1	560	45	252
2	700	41	287
3	430	60	258
	Average	48	266

and 53 mg. per cent. The sixth patient suffered from incontinence of urine; her daily excretion could not be determined but the average histidine concentration in her urine was 36 mg. per cent.

It is important to note that most urine samples of eclamptic patients gave a negative result when tested for histidine with the original method of Kapeller-Adler. This must be attributed to technical reasons.

In severe cases of eclampsia when the disfunction of the kidneys becomes very advanced the excretion of histidine may be diminished. This is not, however, a special peculiarity of eclampsia since it is also observed in advanced nephritis where the excretion may decline to as low as 80-100 mg. per day.

DISCUSSION

The observations described in this communication speak for themselves. Using an improved method every sample of human urine was found to give a positive histidine reaction with bromine. Qualitative estimations of histidine in urine as a pregnancy test have, therefore, no meaning and are not based on fact. Quantitative determinations are of no greater value since the histidine concentration in the urine and its daily excretion were not found to differ significantly between men and pregnant or non-pregnant women.

A diet rich in protein was found to increase the excretion rate of histidine to an approximately equal extent in pregnant and non-pregnant individuals. It is, therefore, doubtful if Page's suggestion (1946) that determination of the increase of histidine excretion after oral administration of a suitable amount of the pure substance may become of practical use as a test for pregnancy.

The claim that in severe eclampsia the excretion of histidine is diminished or that it may even completely disappear from the urine could not be confirmed. In 8 cases of typical eclampsia the excretion was of the same order as in normal subjects on a protein-poor diet. No indication could be found that the metabolism of histidine undergoes any conspicuous change during pregnancy, normal or complicated by eclamptic toxaemia. Therefore, histidine determinations in urine, like those of histamine (Gabrawy, Anrep and Barsoum, 1950), have little value as a diagnostic procedure or for the purpose of studying abnormalities of gestation.

CONCLUSIONS

1. No significant difference in the excretion of histidine in the urine by men and pregnant or non-pregnant women could be detected.
2. The histidine excretion rate mainly depended on the amount of protein in the diet. On a high protein diet the excretion was 500 to 750 mg. and, on a low protein diet, 150 to 300 mg. per day.
3. The excretion of histidine in cases of severe toxaemia of pregnancy was like that of normal individuals on a protein-poor diet.
4. It is suggested that the difference between these results and those of some previous authors is due to the use of the improved method for histidine determination described in the present communication.

The subject of this research has been suggested to us by Prof. G. V. Anrep, F.R.S., to whom we should like to express our thanks for his constant help and advice.

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SYMPHYSIOTOMY

A Study Based on Eleven Personal Cases

BY

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"I tell you quite seriously there is a place for symphysiotomy in carefully selected cases of outlet deformity." (MUNRO KERR, 1948)

SYMPHYSIOTOMY is an old operation. It was practised, often successfully, before Caesarean section became practicable and respectable. It enjoyed two short innings towards the ends of both the 18th and 19th centuries, only to disappear again. The operation still survives in Latin America through the influence of Zaraté and, in the last few years, Alexander Spain has re-established it in Ireland.

This history of alternating revival and decline, of enthusiastic adoption followed by disappointed abandonment is a fascinating story. Throughout two centuries it has engaged interest and provoked controversy among the greatest obstetricians and is not yet a dead subject. Even now as the master obstetricians of the early 20th century are passing from the scene regretting the lapse of the art of symphysiotomy, a few younger spirits of our day are making their own discoveries in this field. This essay, based on a study of 11 personal cases under modern conditions, aims at determining afresh the true scope of this old, simple and most logical operation.

The French physician Sigault is clearly the father of this operation. While a student in 1768 he suggested the possibility and in 1773 he made it the subject of a thesis. Finally he was the first to perform the operation in 1777. The historic patient was a Madame Souchet who had suffered 4 stillbirths. She is said to have had a true conjugate of 6·5 cm. In this the first symphysiotomy she got a live healthy baby but at the expense of vesico-vaginal fistula. The result was regarded as something of a triumph and Sigault was awarded a silver medal by the Faculty of Medicine of Paris. The triumph was ill-digested and the operation was promptly abused. Sigault's 5th case is said to have had a true conjugate of 2 inches and produced a very bad result. Sigault lost heart in the operation of his own invention. Professor Aitken of the Chair of Midwifery in Edinburgh stated in 1786 that the operation had been performed at least 30 times. The operation then seems to have become dead within 10 years and we can assume failures from reckless choice of cases and from damage to bladder and urethra. The latter complication was very important and this induced Professor Aitken (1786) to suggest pubiotomy as an alternative. He believed that the enlargement of the pelvis would be greater and that the urinary tract would be safer by avoiding the midline.

Baudelocque was against these operations and we hear no more of them for about 50 years until Bar le Duc again suggested pubiotomy in 1824 and this operation was first performed by Galbiata in 1832. He was followed by a few other surgeons.

Practically nothing is recorded in the next 50 years but it appears that the operation of symphysiotomy had been kept alive in Italy and Morisani (1881) of Naples reported 50 cases to the International Medical Congress. Spinelli reintroduced the operation to Paris where it was taken up with what seems excessive enthusiasm by Pinard in 1891. Pinard (1894) and Farabeuf (1894) worked hard to develop the theory and practice; Farabeuf studied the anatomy and measurements involved while Pinard did nearly all the operations at the Baudelocque Clinique. Their work was reported to the International Congress in Rome in 1894 and a period of in-

tense activity began in France and in America. It did not last long. Farabeuf's estimates (1894) were too extreme (he allowed symphysiotomy for a true conjugate as low as 7 cm.) and Pinard (1899) had some hard experiences with injuries to bladder, urethra and to the vestibule. Their operation was an "open" one and occasioned severe haemorrhages and frequent prolonged sepsis afterwards. They reported 100 cases in 1899 and thereafter Paris seems to have dropped the operation.

The Germans persisted. They devised subcutaneous methods. Frank (1913) with 113 cases and Kupferberg (1926) with 161 cases had excellent results and preferred this method in feasible cases even to lower segment Caesarean section. Zaraté (1931) followed and improved the operation still further with his partial or intracapsular form of symphysiotomy again using a subcutaneous technique. His operation was easily the best until Alexander Spain devised his new method.

The invention of the Gigli saw in 1894 revived interest in pubiotomy and Döderlein spent some years in perfecting this operation. The wholly subcutaneous method was devised and results were greatly improved. This was the operation adopted by Whitridge Williams. By 1909 Schläfli could collect 700 cases with a maternal mortality of 4·8 per cent.

Williams (1930) thought that the maternal mortality rate was under 2 per cent in the best hands—an excellent figure for that era, comparing favourably, as he said, even with results following early conservative Caesarean section.

Unfortunately, Döderlein (1904) had followed Farabeuf in making excessive claims for the efficacy of pelvis widening operations. He calculated that when the pubic bones gape 6 or 7 cm. the area of the inlet was increased by one half. Such a gap is intolerable and such an increase in area is an exaggeration. It was unfortunate that Morisani, Farabeuf and Döderlein had all agreed on a true conjugate of 7 cm. as the low limit for the performance of pelvis widening operations. Such extravagant claims could only bring discredit to the method and it nearly died out in Europe altogether. It is significant that Williams and Munro Kerr practically abandoned the operation from 1916 except for funnel pelvis. At this point it is illuminating to mention that Zaraté (1926, 1931), who kept the operation of symphysiotomy alive, at least for Latin America and Spain, gave a low limit of 8 cm. for the true conjugate. Alexander Spain, to judge from his published cases, appears to operate on a low limit of nearly 9 cm. and I think the low limit will and should remain at that level. We can be certain that there will never be any attempt to revive symphysiotomy (or pubiotomy) for any but borderline degrees of brim disproportion. For higher degrees of brim contraction Caesarean section is the only answer; but this operation, in spite of all the immediate satisfaction it gives, has several long-term disadvantages especially in certain communities and it need not remain the sole answer to every type and every degree of pelvic abnormality. Frank (1913), who was a great exponent and improver of both Caesarean section and subcutaneous symphysiotomy, preferred the latter operation whenever it was feasible. His epithet for the operation was "segensreichsten"—the "blessed" operation. There is one further point. Severe degrees of brim contraction are becoming fewer and in our day few pelves have a true conjugate of less than 9 cm. Nearly all brim disproportion may become "borderline", in which event it may well repay us to reconsider the potentialities of pelvis widening operations.

Mechanics and Efficiency of Symphysiotomy

I have had the good fortune of finding the most complete study of this subject known to me, that by A. S. Sandstein. His elaborate research formed the basis of his Gold Medal M.D. Thesis (1901) in the University of Edinburgh. Professor A. R. Simpson, then Professor of Midwifery in Edinburgh University, fostered this work as being original and important, providing the materials and directing the study. A condensed version of the Thesis was prepared for publication and is readily available for study (Sandstein, 1902).

Twenty-eight female cadavera were subjected to symphysiotomy and a vast series of measurements was taken at each 1 cm. of pubic separation from 1 to 8 cm. He found that the effect of

separation of the pubes was complicated and he described three separate movements:

1. Movement of the pubes outwards by rotation of the innominate bones on vertical axes passing through their respective sacro-iliac joints. Sandstein's comment is: "although each pubes is carried further from the sacral promontory than it was before by every access of pubic separation, yet it is not so with the line joining the two pubes, which, indeed, in some shapes of pelves, may even be carried nearer the sacral promontory."

2. The second movement consists in rotation of the innominate bones on a horizontal transverse axis passing through the sacrum, and carrying the pubes downwards. This is, of course, counter-nutation of the sacrum and is actually an exaggeration of the movement occurring in Walcher's position.

3. The third movement (described for the first time by Sandstein) consists in rotation of the innominate bone on its own long axis, i.e. an axis lying in a direction from the posterior superior iliac spine to the iliopectineal eminence. The result is that the upper part of the innominate bones moves inwards towards the middle line, while the lower part revolves outwards, increasing still further the transverse diameters of the outlet. The movement is clearly illustrated by the attached copy of Sandstein's drawing (Fig. 1).

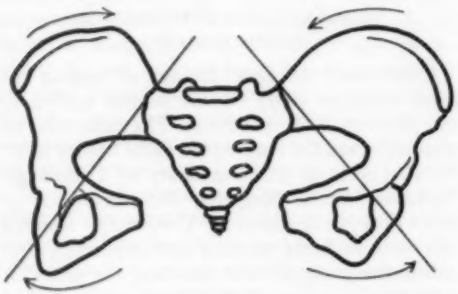

FIG. 1

Sandstein's 3rd movement. Traced from Sandstein's original sketch.

Sandstein's attention was chiefly directed to the effect on the measurement of the true conjugate and I give his table:

Pubic Separation centimetres	Increase in Conjugate Vera millimetres
1	1·67
2	3·34
3	5·01
4	6·68
5	8·35
6	10·02
7	11·69
8	13·36

Roughly speaking, according to Sandstein's direct measurements, it requires 6 cm. of pubic separation to give an increase of 1 cm. in the true conjugate. It should be noted that this is an average and *may be much less in a small pelvis.* Further, Sandstein concluded that in the majority of cases this increase in the conjugate was more attributable to movement 2, i.e. counter-nutation than to movement 1, i.e. separation. Here are his actual words: ". . . it appears that the true significance of the division of the symphysis during labour in order to increase the true conjugate lies mainly in the fact that it thereby permits increased descent of the pubic bones from their horizontal level. This would lead to the conclusion that symphysiotomy is really a means of obtaining greater effects than we can by Walcher's position." Sandstein suggested that, following symphysiotomy, the patient should be allowed to proceed in labour in the Walcher position with support to the sides of the pelvis. Such a laborious, painful and even dangerous form of management of brim disproportion is in our time unthinkable. I feel that Sandstein went wrong in his calculations by accepting the general estimates of the value of the Walcher position as they were believed at that time. Since then, X-ray studies have shown that the Walcher position is in fact valueless. I quote Brill and Danelius (1941): ". . . the results would indicate that in the average the length of the true conjugate comparing a comfortable dorsal position with Walcher's position shows a negligible change of about 0·25 cm.—shortening occurs twice as often as lengthening."

Unfortunately, Sandstein did not measure directly the increment of the true conjugate with the cadavera in the lithotomy position or in the

half-lithotomy position which I have used while dividing the symphysis. (In this position I have not noted any descent of the pubes.) Further, on inspecting X-ray views of the pelvic brim it seemed to me that all pelves would show at least some increase in the true conjugate from simple separation of the pubes and that some, especially with a beaked forepelvis, would benefit considerably. I think it is possible to measure approximately the increase in the true conjugate by making a simple geometric construction on the X-ray antero-superior view (see Appendix and Table). I have done this on 100 X-ray films measuring against a 5 cm. separation of the pubes. The average figure for the 100 constructions is an 8 mm. increment with variations ranging from 5 mm. minimum to 11 mm. maximum. The higher values are consistently found in the flat pelves, the low values in the round or long oval pelves.

The average increment for pelves with a brim index under 80 per cent is 9·5 mm., while the average for pelves over 90 per cent brim index is 7 mm. The smaller pelves show the smaller increments. For convenience, these results are tabulated. In general, then, the operation does not help greatly in increasing the true conjugate and so cannot have much to offer in the general management of brim disproportion.

INCREASE IN TRUE CONJUGATE AFTER PUBIC SEPARATION OF 5 cm.

Average increase (100 cases) ..	8 mm.
(minimum 5 mm.; maximum 1·1 cm.)	
For flat pelves under 80 per cent P.I.	
Average in 15 cases	9·5 mm.
For round pelves over 90 per cent P.I.	
Average in 22 cases	7·0 mm.

But this is not the whole story. Sandstein further elicited the facts that the transverse diameter of the brim was increased by 4 mm. per cm. of pubic separation and that the oblique diameter was increased by about 3·8 mm. The average increments with a 5 cm. separation would be 2 cm. and 1·8 cm. respectively. These are worth while increases and in a small round pelvis with inadequate transverse measurements at the brim could be very effective. When there is a combination of beaked forepelvis with poor transverse measurements at the brim, the prospects for symphysiotomy for brim disproportion are at their best. I think this is shown in many of Spain's and Barry's examples of the operation for the unengaged head.

Before leaving Sandstein's thesis there are a few valuable points to extract. He set himself to discover the safe limit of the operation. Studying the effects of extreme pubic separation on the cadavera he came to the opinion that "the danger of separation of the pubes had no reference at all to the sacro-iliac joints".

Disorganization or subluxation of the joint did not occur at any degree of pubic separation. Tearing of the anterior and superior ligaments only begins with a 7 cm. separation and then only in non-pregnant cadavera. Pinard had the same finding. These ligaments merely form a thin sheet covering in the joint above and in front. In pregnancy they soften and stretch well. Pinard pointed out that in pregnant cadavera occasionally a little tearing of the periosteum was noted just lateral to the salient angle of the sacro-iliac joint and that these feeble anterior and superior ligaments never suffered damage. The only important ligaments for binding the bones together are the posterior sacro-iliac and greater and lesser sacro-sciatic ligaments—and these are actually relaxed during symphysiotomy.

Sandstein's contention is completely borne out clinically by the fact that difficulty in locomotion is not a sequel to symphysiotomy. Zaraté and the Latin-American school bear this out and in our own islands Spain and Barry and I have had no such sequel nor any cases of sacro-iliac joint pain.

On the other hand, Sandstein showed that the whole stress of the operation fell on the soft tissues. He was impressed by the great tension on the vestibule of the vulva. Up to 6 cm. separation the vestibule takes the strain well, but at 7 cm. separation and upwards the structures between the labia are stretched very tensely and are thrown into ribbed folds. He set a limit of 6 cm. separation. This agreed with the findings of Pinard and Farabeuf. Döderlein, however, set the clinical limit of separation at 5 cm. and is followed in this by Frank (1913), Zaraté, Spain and Barry. This limitation is purely in the

interest of the vestibular tissues which alone are vulnerable in this operation. *The bladder and urethra are not affected by separation unless by an extension of a vestibular tear.*

The last point which I wish to take from Sandstein's Thesis is his third movement, i.e. rotation of the innominate bone on its own long axis. This has the effect of carrying the tubera ischii further apart than simple separation would do. And it is precisely this effect of pelvic outlet widening which we require to overcome outlet contraction. The effect of separation of the pubes on the intertuberischial diameter has not been measured, but it is the most astonishing single phenomenon in performing delivery after symphysiotomy. For a 5 cm. pubic separation I believe that the intertuberischial diameter is increased by about 4 cm.

The Operation

The operation, as I have practised it, is based on the recommendations of Alexander Spain. As modified to suit my own instruments and hands I find that my operation is near that of Zaraté and can be described as a partial symphysiotomy, leaving intact the arcuate ligament and as much as possible of the lower third of the posterior ligament of the joint. The anterior clothing of the joint by the interlaced decussation of fibres derived from tendons of adjacent muscles, especially of the rectus abdominis and external oblique muscles, is left intact as far as possible. I shall describe the operation as it applies to a vertex presentation with the head well engaged, the os fully dilated and after failure to deliver by forceps on grounds of outlet contraction.

The patient is placed on the table in a semi-lithotomy position. The legs are held by two assistants, who sit firmly braced against the sides of the patient's pelvis, the thighs being maintained at about 45° flexion and about 30° abduction. The pelvis rests on a symphysiotomy corset. All but one of my cases have been conducted under spinal analgesia. When immediate delivery is indicated, it is an advantage to leave the obstetric forceps in position.

A transverse incision about 4 cm. long is made just above the upper border of the symphysis pubis and the tissues are divided down to the rectus sheaths. This is the only part of the operation where any bleeding is encountered and superficial vessels may occasionally have to be secured. The rectus sheath is divided longitudinally upwards for nearly 2 cm. and transversely in each direction at the upper border of the symphysis for 1 cm. These incisions must be made cautiously as the bladder and urethra may be very closely applied to the upper border of the symphysis at this stage of the operation. The left index finger is then pushed readily into the space of Retzius between bladder and symphysis. The finger is pushed right down to the arcuate ligament and so displaces bladder and urethra backwards out of harm. Occasionally I have temporarily introduced two fingers behind the symphysis for the greater mobilization of these organs. If the head is very tightly jammed in the pelvis an assistant can ease matters by gently pushing the obstetric forceps upwards and I regard the retention of the obstetric forceps as a very marked help in this respect.

The next step is to locate the joint and this step is by no means automatic. The joint is generally displaced slightly to the left and may be as far away from the midline as 1 cm. The joint is located by a tubercle on the superior border of the symphysis and by a ridge down the back of the symphysis. The knife must cut through the summit of both tubercle and ridge when cutting will be found to be very easy. If the exact centre of the fibrocartilage plate is missed, the cutting can be very hard work. The knife, which should be a solid scalpel, is introduced on the flat between index finger and symphysis then turned against tubercle and ridge. Care is taken to ensure that the knife is held exactly longitudinally. The scalpel is then firmly pressed forwards by the index finger in the space of Retzius. It is an advantage to rock the scalpel slightly by depressing the handle backwards against the patient's abdomen. I find I can now cut through the upper two-thirds of the symphysis in one step. When this has been completed the symphysis already opens about a $\frac{1}{2}$ cm. The scalpel is withdrawn and the exploring finger feels for the upper edge of what is left of the posterior ligament. In its upper two-thirds, the posterior ligament is flimsy and is of necessity cut; in the lower third of the symphysis the posterior ligament is much stronger and its sharp edge can be readily pal-

pated. I feel for this sharp edge and reinsert the scalpel just anterior to it and then complete the cutting of the fibrocartilage, working as always from behind forwards. During this process the symphysis gradually opens a full 1 cm. and the index finger can readily feel the gap made. The scalpel is then withdrawn.

The assistants then flex the thighs to 90° and are required slowly to abduct the thighs to about 45° when the symphysis separates slowly to about 4 cm. This is generally an adequate gap. The abduction is done slowly and equally on the two sides and the movement is checked by two fingers in the symphyseal gap. The arcuate ligament can be palpated in the depths of this gap and about 1 cm. of the posterior ligament. I believe it is important to leave this ligament intact. It protects the vestibule from tearing by violence, just as a hem protects a handkerchief. It is also an insurance against severe haemorrhage from the vessels to the clitoris. This is an essential Zaraté principle.

In the conditions given above, the patient is ready for delivery. In 2 of my cases delivery was readily completed by Kristeller expression. In 8 others the already applied forceps were used and in this connexion I would generally advise to deliver exactly as the head is lying without imposing attempts at rotation. In all but 2 of my cases at the time of pubic section the Kielland forceps have been in a classical application with the head in transverse arrest.

The chief effect of a symphysiotomy is the generous increase in the transverse diameters of the outlet. According to Kerr and Moir (1949) this increase is so great as to equal the width of the symphyseal gap. Thus, with a 4 cm. gap, which implies nearly a 4 cm. increase in the intertuberischial diameter, this diameter will be much greater than the antero-posterior of the outlet. Advantage, then, should be taken of this situation to deliver the head as it lies. As the head approaches crowning the forceps are removed and the baby is delivered by expression. The head usually rotates spontaneously just after crowning. It has to be remembered throughout that the vestibule is under great strain and for its protection a large episiotomy is made and the head brought down more posteriorly than usual.

After the whole delivery has been completed the episiotomy is repaired and a self-retaining catheter is introduced. (This will be allowed to remain in the bladder for 4 days.) The patient is then restored to a dorsal position with the legs together while the symphysiotomy wound is secured by 3 or 4 deep silk sutures. The symphysiotomy corset can then be tightly buckled up and the patient returned to bed. The symphysiotomy corset is not, apparently, essential. Frank and Zaraté were content merely to tie the knees together. I think the corset gives greater comfort and gives the nursing staff more confidence in handling the patient. It can be omitted after 4 days and the knees tied together to the end of the first week. The patient is kept in bed for 14 days and her ambulation is generally satisfactory on her discharge at about 21 days. By this time the symphyseal gap averages 1·5 cm.

The Applications of Symphysiotomy

I have classified the indications for symphysiotomy into 4 groups:

1. The engaged head arrested by mid-pelvic or outlet contraction.
2. The engaged head arrested in an abnormal presentation as face or brow.
3. Breech presentation.
4. Disproportion at the brim.

The first I would place as the ideal indication for symphysiotomy. Williams retained this indication in his latest text-book and as late as 1948 Munro-Kerr was declaring that there was a place for this operation in outlet contraction. Feeney (1947) and Spain began the revival in Ireland with just these cases. They are not very common, and it has taken me 4 years to employ the operation in 9 ideal cases. Five of these came as emergencies from outside where the attendant, having found an engaged head with full dilatation, had been unable to obtain the expected normal or easy forceps delivery.

In hospital practice, too, it is quite easy to miss outlet contraction and so find that a very sudden emergency arises with the head practically within sight. When the operator has no recourse to symphysiotomy the tendency will be

to over-severe use of the forceps and an apparently simple low forceps may end in craniotomy.

The most gratifying use of the operation occurs in face of a known outlet contraction. These outlet contractions are notoriously difficult to measure and it is still more difficult to estimate their effects on labour. Nearly every case of outlet contraction can be dealt with by trial of labour and trial of forceps *but only if symphysiotomy is available*. One can be very confident if the defect is in the transverse diameters: but extreme forms of antero-posterior shortening require very careful consideration. An example is my case No. 10. Here was a well shaped pelvis, whose smallest conjugate, in this case the true conjugate, was 11·3 cm. with a brim index of 88 per cent. The only defect was the sub-pubic arch of 58°. I employ the Peter Allen system of measurements but use a 92 mm. circle instead of his 100 mm. circle for the sub-pubic estimations. In this case there was a symphysis-biparietal diameter of 9·0 cm., the highest I have ever measured. This reduced the Allen's post-sagittal diameter to 5·3 cm.—one of my very lowest. Because of all the other excellent features of this pelvis I allowed trial of labour and trial of forceps. After a very tedious labour she came to full dilatation and to deep transverse arrest. A Kielland forceps operation with full episiotomy failed as was expected and the symphysis was then opened. I attempted to deliver at various stages of separation but the head did not move until a full 5 cm. was reached. The head then came down easily, rotated while crowning and was easily delivered by fundal pressure. Mother and baby made an excellent recovery. This was not my most satisfactory case. The separation of the pubes was the widest I have had to make and the vestibule must have been in some danger of rupture. No doubt the Gothic arch was converted into a Norman one but even so the increase in antero-posterior diameters is always disappointing in symphysiotomy and strain falls on the vestibule.

Even more satisfactory is the security afforded in allowing trial of labour and trial of outlet forceps if symphysiotomy is available. I quote another case where vaginal delivery would have been a perilous gamble without this operation in reserve. The X-rays showed a small nearly round pelvis with many excellent features but badly spoiled by a sub-pubic arch of 69°. With our 92 mm. S.O.B. circle this showed a sub-pubic wastage of 3·6 cm. Clinically, the intertuberischial diameter appeared to be about 3 inches (7·6 cm.). Because of the excellent hind-pelvis I fortunately allowed trial of labour and trial of forceps. After a most tedious and irregular labour lasting just on 3 days she arrived at full dilatation and then remained in deep transverse arrest. I was quite certain that a symphysiotomy would be necessary as there seemed to be very little room for the hand to work in.

I had my assistant attempt the forceps delivery. She was able to make the manual rotation and applied forceps. After a prolonged and very severe traction the baby weighing 6 pounds 5 ounces was delivered in fairly satisfactory condition. The forceps traction was laconically described by my assistant as "the limit".

The sequel is worth recording. Two years later she had a second pregnancy. On this occasion the labour was of the first quality. The first stage only lasted 8 hours and the second stage was completed spontaneously in under 1 hour. The baby was just over ½ pound heavier than the previous one.

A similar case is quoted by Williams and Arthure (1949). The lower A.P. diameter was 10·2 cm., the corrected lower A.P. 8·2 cm. (!) and the ischial bispinous, 8·2 cm. (!) It was at first considered that vaginal delivery would be impossible after examination under anaesthesia. Mr. Gibberd, who conducted the case, allowed a vaginal delivery with preparations made for symphysiotomy. Eventually forceps were applied, the head being fully rotated. "Extreme traction was necessary and delivery was eventually accomplished." The baby weighed 7 pounds 6 ounces. The moulding was extreme. A second vaginal delivery was allowed after induction at 37th week in the next pregnancy. A smaller baby weighing 6 pounds 8 ounces was delivered by more moderate traction. I note that the area of the outlet by the measurements given was only 53 sq. cm., which was exactly the area of the sub-occipito bregmatic circle. A symphysiotomy, had it been necessary, would have increased the outlet area to just over 80 sq. cm. given a full 5 cm. separation.

Large series of symphysiotomies are reported from time to time from Spain and Latin-America. A most interesting series is reported by Baens (1946) from the Philippines. In his 64 cases with excellent results and no complications all his indications are for the engaged vertex, usually after failed forceps. Apparently he does not extend his indications beyond this type of case. The largest series I know is reported from Beunos Aires by Peralta Ramos (1948). He discusses 412 cases with no maternal mortality. It has to be noted that this series covers a period of 1913-48 and only represents an incidence of 2·2 cases per 1,000. The indications are very strictly watched. In 1931 and 1932 the Buenos Aires school widened their indications but promptly ran into both foetal and maternal accidents and returned to a stricter path. They use the operation for the engaged or nearly engaged vertex cases and do not deliver immediately. They find that spontaneous delivery usually follows in half an hour. They are very chary of the operation for primigravidae and only use it for the most favourable conditions of the soft parts.

A Barcelona series of 161 cases is reported by Vallhonrat (1948) and represents 22 years' work. He is less strict than the Buenos Aires school in the indications. He prefers in theory the operation for multiparae but I note 70 per cent were for primigravidae. His figures include symphysiotomies for 18 breech presentations and 9 for face or brow cases. The results are correspondingly poorer.

The very best results will be obtained by restricting the operation to engaged vertex cases arrested by outlet contraction. I note that Barry (1952) now calls this a Classical Symphysiotomy.

The second indication is for the engaged head arrested in the pelvis as a face or brow. Again all the operators who have used it are very satisfied. Zaraté had 9 such in his 100 reported cases. Naturally it is an indication which seldom occurs. I have only been able to employ it for 1 case. This patient, a primigravida, was admitted from some 40 miles away in obstructed labour, fully dilated and the head within sight. She was in violent labour with a well marked retraction ring. The foetal heart was present but slowed to 100 and irregular during contractions. Examination showed a deeply impacted brow. The head was so low that a direct forceps delivery was immediately attempted. This failed, the resistance being absolute. The symphysis was opened to 4 cm. In this case the forceps had been removed and my sister, who was also my anaesthetist in this emergency, readily pushed the baby out by Kristeller expression. It was secured in good condition and weighed 7 pounds 5 ounces. In this case the patient had an outsize in pelves and had not been far from delivering herself spontaneously as a brow. Two years later I heard that she was again pregnant. She was now living in a remote district and again elected to be delivered at home. A rather similar emergency occurred in the second stage and a flying squad had to go to her rescue. On this occasion an obstetrician found a deeply impacted face presentation from which the patient was easily delivered by forceps.

I am able to concur with all other symphysiotomists that this very occasional indication is a most satisfactory one and well worth remembering in the late case when correction or improvement of the presentation is impossible.

The third indication is breech presentation.

Around the year 1900 breech presentation was considered a proper indication. Pubiotomists used it regularly. Indeed in border-line cases Williams had the pubiotomy saw placed prophylactically against undue difficulty. Zaraté continued to practise symphysiotomy for difficult breech cases and in his report of 100 operations 10 were for breech. The Barcelona series of 161 contains 11 per cent of breech cases. It is not used, however, for primigravidae.

I have no doubt that symphysiotomy might give a good result for a multiparous breech with a transversely contracted pelvis—Barry (1952) includes 1 in his series of 42 cases, while Alexander Spain (1949) actually reports a prophylactic symphysiotomy for breech presentation which gave an excellent result. But a very great danger might arise if a breech extraction became necessary. The added bulk and the active movement of the hand and wrist might well cause a vestibular tear. The danger to the mother is too great.

Occasionally, however, the operation has been used for failure to deliver the after-coming head.

I have already mentioned that Williams kept a pubiotomy saw in place for this eventuality. Symphysiotomy can be done so quickly that it could be used. The actual section of the pubes only takes about 1 minute in an easy case.

The fourth indication is for the non-engaged head.

This brings us to the most difficult ground. The operation was hopefully devised for brim disproportion and despite all the improvements made in the technique around 1900 it had to be virtually abandoned as a failure. To begin with, Pinard was allowing the operation with a true conjugate as low as 7 cm. This figure was commonly accepted. Ayres (1897) went as low as 6·5 cm. In time the limit was raised. Zaraté put it at 8 cm. But even that is too low. The operation is used in Barcelona for the non-engaged head and, very cautiously, in Buenos Aires. There they use this indication only for multigravidae and where they feel certain that the slight increase in the true conjugate will just turn the scale. They do not lay down a precise measurement.

Nevertheless, Spain first and now Barry have succeeded in widening the scope of symphysiotomy. They have the special circumstances of treating an almost solidly Catholic population and they are in hopes of averting many sequences of repeated Caesarean operations when the pelvic contraction is not too extreme. The last report of the National Maternity Hospital in Dublin which I possess is for 1948 and it seems to show that about 50 per cent of their *new* cases of disproportion were treated in that year by symphysiotomy. At that Spain thinks the full scope of the operation has not yet been reached. Similarly, in Latin-America and in continental Spain the obstetricians there have their own special reasons for avoiding Caesarean section. Aynié (1949) from Madrid reports that the incidence of voluntary infertility after Caesarean section is at least 50 per cent and quotes other authorities who place it as high as 70 per cent. Ramos from Buenos Aires reports the incidence as 50 per cent. These workers have therefore a strong incentive to apply symphysiotomy, after which operation the pelvis is permanently improved in capacity and subsequent labours are very frequently spontaneous.

The operation for brim disproportion can be applied in two ways. It can be applied in the midcourse of labour especially when abnormal uterine action and delayed dilatation are believed by the attendant to be essentially due to the disproportion. The symphysiotomy is performed, the wound is closed and the patient continues a normal labour in the dorsal position. If the cervix is nearly fully dilated, Ramos expects the head to descend into the cavity within half an hour, whence it can be delivered by forceps if need arises. Generally, spontaneous delivery is obtained and perineal lacerations are very rare because of the great outlet widening. It can also be applied in early labour. Spain does this and calls it prophylactic symphysiotomy. Further, he has actually used surgical induction and prophylactic symphysiotomy before the onset of labour. Spain does not fix a low limit for the true conjugate in his practice, but from reading his case histories it would appear to be about 9 cm. Barry mentions 8·5 cm. as a low limit but clearly these figures can only be rough guides as other considerations of age, parity, presentation, size of foetal head as well as pelvic shape come into the picture. In any case, only experienced obstetricians with constant practice in the management of contracted pelvis should consider using symphysiotomy for disproportion at the brim. The practice must be supported by full X-ray pelvimetry, and, where possible, cephalometry. Further, I would suggest that the antero-superior X-ray of the pelvis be studied and that the geometric construction which I have outlined should be applied so that some measure of the effects of pelvis widening can be obtained.

I have experience of this form of management in only 1 case and I have to admit that it was very satisfactory. It was not a carefully premeditated case, but one forced on me in emergency circumstances. This was a primigravida suffering from a moderate degree of pre-eclampsia. Several medical inductions had failed and I had not attempted surgical induction because of a high head and a high tight cervix. An X-ray pelvimetry showed a round pelvis of fairly good size. The main defect was a subpubic angle of 68° but this appeared to be redeemed by other good outlet measurements. There was beaking of the forepelvis and I probably underestimated the significance of this.

She came into labour spontaneously at 40 weeks. Early labour was poor and erratic but the head fixed well and normal descent was expected. After 48 hours in weak irregular labour she had 2 mild eclamptic fits. I examined her under pentothal anaesthesia and found the cervix with a taut rim only half-dilated. A large caput reached the spines but the head was about 1 inch above. The head was in a badly flexed L.O.L. position and the greatest diameter was still just above the brim.

Instead of bringing her by ambulance to my main hospital (Caesarean section was not possible at the nursing home where she lay) I elected to perform a symphysiotomy. A gap of 4 cm. was allowed and labour was continued. Four hours later she had an easy spontaneous delivery of a live baby weighing 8 pounds 8 ounces. X-ray photographs were taken 16 days after delivery when the symphyseal gap was still about 3 cm. These demonstrated the improvements in the shape of the forepelvis, the rounding of the sub-pubic arch and the great transverse widening of the ischial tuberosities with a relatively small separation of the symphysis. The indication here was bad pelvic shape and bad uterine action with time running out. The immediate improvement in the quality of uterine contractions was exactly as described by Spain and Barry.

Conclusion

My experience is small—only 11 cases in 4 years—but I do claim that there is a place for this operation; that when it is performed in the right case it gives a satisfaction rarely equalled in my experience. We have all had to regret the use of some excess of force in forceps extractions or alternatively we may have applied rather grudgingly the ultimate sanction of the Caesarean section to cases wherein we felt that the indication was only present by a very small margin. In such circumstances symphysiotomy can be a valuable instrument. It allows fuller scope to trial of labour, gives an easy escape from a severe or failed forceps, and avoids the future limitations imposed by Caesarean section and permanently enlarges the pelvis for future occasions. It is an operation, as Munro Kerr says, of true obstetric finesse.

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APPENDIX

When symphysiotomy is being considered for small degrees of brim disproportion it is clearly desirable to be able to estimate what gain in the value of the true conjugate is likely to be obtained. As this value varies from case to case and is not capable of being estimated by any formula, a tracing of the X-ray of the pelvic brim should be studied. Further help is got by having the radiologist mark the X-ray picture of the brim with his known reduction factor. This is usually 1/1·2 when films are taken at 100 cm. tube-film distance but the exact factor is always known to the radiologist and should be used.

A simple method of measuring the expected increase in the true conjugate is illustrated on the next page (Fig. 2). The anterior ends of the sacro-

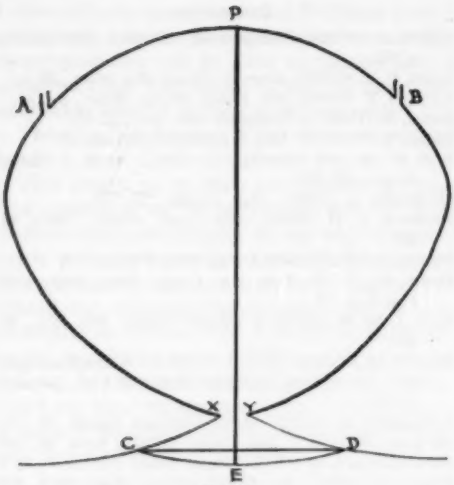

FIG. 2

Tracing of Brim X-ray Contour and simple geometric construction for determining increase of true conjugate given by a 5 cm. symphyseal separation.
Reduction factor is 1/1·2.

iliac joints are marked A and B, the inner margins of the extremities of the pubic bones are marked X and Y. Circles are traced outwards using AX and BY as radii. A line CD is then drawn at right angles to the true conjugate joining the two arcs. The length of this line is determined (*a*) by the amount of pubic separation which is to be allowed and (*b*) by the reduction factor peculiar to the pelvic X-ray studied. For example, if a pubic separation of 5 cm. is contemplated and if the reduction factor is 1/1·2, then the line CD will be drawn as 6 cm. (5 × 1·2). Another arc of a circle is drawn with its centre at the promontory (P) and its radius the average between PC and PD. This arc joins C and D. The point E is marked as the centre of this arc and PE then represents the new true conjugate after pubic separation. This line is measured, the reduction factor applied and the post-symphysiotomy true conjugate is obtained.

POSTSCRIPT

Since completing this paper a 12th symphysiotomy was performed, which led to grievous maternal injury and it seems proper to report this as illustrating the extreme caution which should be adopted in carrying out this operation.

The patient was a robust stout young woman in her first pregnancy. Her height was 5 feet 4½ inches and her standard weight was generally around 11 stones. When examined in late pregnancy she was found to have a very large pelvis, whose only mild defect was a long, rather straight sacrum. In the last 2 weeks of pregnancy her very stout abdomen became even larger by reason of hydramnios and she developed mild pre-eclampsia. She was allowed to go to her due date exactly and then had a surgical induction by low rupture of membranes.

This produced a good labour, in which the first stage was completed in some 15 hours and she was then left in the second stage for approximately 6 hours, but with failing uterine contractions. The head was then well down in the pelvis in almost a complete occipito-posterior position.

A forceps extraction under spinal analgesia was undertaken. After various manœuvres, the last of which was an attempt at a Kielland forceps extraction from a deep R.O.L. position, the operation was abandoned as a failure.

The head did not seem unduly large for this big woman with a fine pelvis and I decided to make use of symphysiotomy to complete the extraction. Leaving the Kielland forceps *in situ*, this was done, following the usual technique and with a 4 cm. gap the extraction of the head was easily completed—this without any damage to the maternal tissues. I was then faced with shoulder dystocia and found myself quite unable to deliver the shoulders by the usual methods. Unfortunately, I was finally forced to resort to putting my whole hand into the lower uterine segment and bringing down the posterior arm and shoulder. The difficulty did not end there and I still had the greatest difficulty in delivering the anterior shoulder. This finally emerged abruptly and in that instant the patient suffered a complete vestibular tear.

The injury was very extensive and included tearing of the urethra from its insertion into the bladder. There was little or no bleeding and I was able to perform an immediate repair. The urethra was stitched into the bladder and a self-retaining catheter was secured in position. The

base of the bladder was further repaired towards the right side and finally the anterior vaginal wall was repaired as far as I could reach it. The catheter was left in for 10 days and for a few days thereafter bladder control was quite good. By the 14th day, however, it was clear that the patient had sustained a fistula and thereafter there was practically constant leakage. The fistulous condition remained for some 5 months until she had a successful one-stage repair of a right-sided vesico-vaginal fistula by Dr. John Sturrock and Mr. David Band. The result of their repair has been a complete success.

The male infant, which was born in excellent condition, weighed 12 pounds 14 ounces. The biparietal diameter on the day of birth was 4 inches and on the following day 4·2 inches. The great weight of the baby seemed to be entirely due to the gross size of its trunk. It made excellent progress on artificial feeding and is well to the present time, though it is still exceptionally large for its age.

The failure to diagnose the presence of a grossly overweight baby was partly due to the patient's stoutness and to the excess of liquor near term and probably to some extent to the fact that, in spite of the occipito-posterior position, the uterus was able to bring down the head to full engagement in some 15 hours.

It is clear that a strong contra-indication to symphysiotomy is the presence of an oversized baby.

THE ASYMMETRICAL PREGNANT UTERUS

BY

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IN an interesting paper dealing with angular pregnancy Fitzgerald (1952) introduces his subject as one of the small but interesting corners of obstetrics occupied by an entity whose very existence, even as a rarity, is questioned. He quotes Miles Phillips as stating that "lop-sided" pregnancies were not uncommon but that they righted themselves at about 16 to 20 weeks. This brief and fragmentary presentation of cases is not so much a contribution to the sparse literature devoted to angular pregnancy as an attempt to show the difficulty of interpreting the significance of the abnormality so aptly described by Miles Phillips.

Asymmetry of the pregnant uterus, rare as it may be, raises rather important points in diagnosis and for this reason is worthy of something more than a place in the purely academic category of "Res Obstetricae". According to De Lee and Greenhill (1949) asymmetry of the uterus occurs in early pregnancy because one lateral half is thicker than the other (Piskacek's sign), or because either the anterior or the posterior wall bulges out more, these variations being due either to the location of the ovum or hormonal influence. They also mention the asymmetry produced by angular pregnancy, emphasizing the difficulty of differentiating this condition from interstitial pregnancy and the re-establishment of symmetry with the later development of the embryo. Hyams (1953), in his description of unruptured interstitial pregnancy, states that the asymmetry of the uterus in these cases is most marked during contraction of the muscle and may not be recognizable when the muscle is relaxed.

The conditions of pregnancy in which asymmetry of the uterus may occur as a phenomenon of clinical significance would seem to be as follows:

1. Pregnancy in a fibroid uterus.
2. Pregnancy in a maldeveloped uterus.
3. Angular pregnancy.
4. Interstitial pregnancy.

The following case history is presented here to show that marked asymmetry can also occur for no apparent reason. To this type of case the description "lop-sided pregnancy" is most accurately applied since the term conveys no indication of the underlying pathology.

Mrs. F., para-1, aged 36 years, was first seen in the antenatal clinic on 11th July, 1952, when she was about 30-weeks pregnant. There had been no bleeding in early pregnancy nor any complaint suggesting abnormality. The foetal parts were easily palpable and a vertex presentation diagnosed. The uterine enlargement did not correspond with her dates and was greater than expected. She was sent for X-ray examination and the radiologist reported "Single foetus, vertex presentation, L.O.L. position. The size of the foetus corresponds with the E.D.C. but the uterus is not symmetrical showing a prominence on its upper part which is not occupied by foetal parts and may be a fibroid." It is noteworthy that, although this asymmetry was very obvious radiologically, it was not so clinically and its recognition by palpation was only made after inspection of the X-ray plates (Fig. 1). We were reluctant to accept the diagnosis of a fibroid because we felt that a tumour of this size and so situated, even softened as it sometimes is in pregnancy, would almost certainly be palpable, which it was not. Moreover, foetal parts were clearly palpable around the whole contour of this so-called prominence. The possibility of this being a case of pregnancy in one horn of some type of double uterus seemed a more likely explanation of the asymmetry. In 1947 the writer delivered this patient by

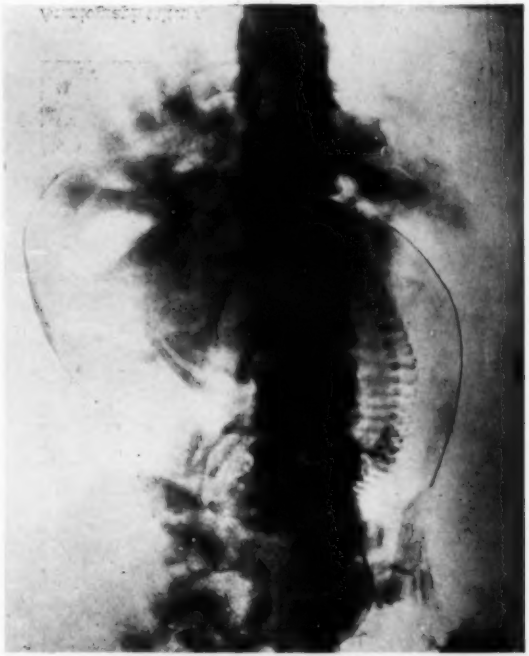

FIG. 1
Asymmetrical uterus 32-weeks pregnant.

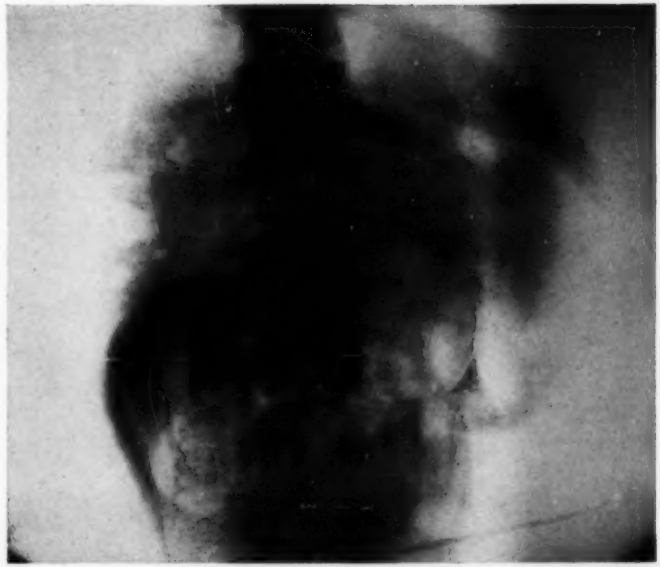

FIG. 2
Amniograph taken at 36 weeks which shows a diverticulum in left cornual angle containing the placental site.

J.B.

FIG. 3

Amniograph taken at 32 weeks which shows a sacculation of right cornual region devoid of the placental insertion.

FIG. 4

Amniograph showing pregnancy in bi-cornuate uterus.

Caesarean section, the indication being contracted pelvis, and on that occasion there was no reason to suspect any abnormality of the uterus. At the same time, the lower segment operation had been performed without any examination of the uterus, and we knew from a previous experience that it was possible to miss a bi-cornuate type of uterus at this operation unless it was particularly looked for. Hypertension made its appearance in the last month of pregnancy and a lower segment operation was again performed on 14th September, 1952, asymmetry being maintained to the end. After opening the abdomen a hand was passed over the fundus and its smooth contour followed without finding any break or indentation to suggest congenital malformation. The placenta occupied the posterior wall and after its removal the uterine cavity was carefully explored for some septal defect but none was found. The infant weighed 6 pounds 8 ounces (2,941 g.).

The cause of asymmetry in this case remains obscure. The patient was of small stature, 4 feet 7 inches (1·4 m.), and there was evidence of the effects of rickets but this fact can have no bearing on the aetiology of an asymmetrical pregnant uterus. Nearly 30 per cent of the women admitted to this hospital are no more than 5 feet (1·52 m.) in height and many of these have been the subjects of rickets, yet we have not previously seen a case such as this.

Dr. W. G. MacKay, consultant obstetrician for the county of Renfrewshire, was greatly interested in this case because it recalled to mind 2 slides which he had made from X-ray plates taken when, as assistant to Prof. Munro Kerr, he was investigating the possibilities of amniography in locating the position of the placenta. The writer is indebted to Dr. MacKay for Figs. 2, 3 and 4, and the following notes on the relevant cases are his.

The patients (Figs. 2 and 3) were remarkably similar clinically, both being primigravidae who had experienced painless bleeding in the last trimester of pregnancy, and in each of whom the foetus presented by the breech and the cervix was not effaced.

Amniography was resorted to in order to establish the site of implantation of the placenta. No unusual asymmetry of the uterus was suspected on abdominal palpation. The resulting films showed a striking enlargement of one cornual region of each uterus.

In the case depicted in Fig. 2 the left cornu appeared to be transformed into a bulbous diverticulum containing the placental insertion. After the birth of the child, which occurred naturally, the placenta was retained and had to be removed manually from a pocket opening off the main cavity of the uterus.

The other patient (Fig. 3) exhibited a more conical sacculation of the right cornual region which did not affect the delivery process in any way. The placenta was inserted normally on the posterior wall of the uterus.

Fig. 2 is presumed to represent a case of angular pregnancy and Fig. 3 an example of simple asymmetry due to disproportionate stretching of a congenitally weak horn by the expanding products of conception.

In both instances the appearances are conspicuously different from those which one has observed in amniographs of bi-cornuate uterus (Fig. 4) in which the fundus is broad and notched and the cornual regions flat.

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BLOOD LOSS FROM THE FOETAL CIRCULATION: A HAZARD OF LOWER SEGMENT CAESAREAN SECTION IN CASES OF PLACENTA PRAEVIA

BY

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IN May, 1951, an infant died in this hospital at the age of 3½ hours from shock due to loss of blood from the foetal circulation, which had been damaged by the operator during delivery by lower segment Caesarean section in a case of placenta praevia. This avoidable death occurred in spite of the fact that we had encountered this complication of Caesarean section on several occasions previously, and had had to give blood transfusions to babies suffering from blood-loss due to this cause. It brought home to us our lack of the fundamental knowledge on which appropriate treatment should be based. We were unable to find any comprehensive account of the problem at that time, and although articles by Wickster (1952) and Siddall and West (1952) have drawn attention to the danger, they have not met the need for this fundamental knowledge about the prevention, recognition, and treatment of the condition. We are therefore reporting the results of a study of the whole problem, carried out by members of the obstetric and paediatric staffs of this hospital, and designed to enable us to do three things:

1. To assess the chances of placental tissue being encountered by the uterine incision when the lower segment operation is performed as a routine in cases of placenta praevia delivered by Caesarean section.

2. To decide the best technique for the delivery in such cases so as to avoid loss of blood from the foetal circulation, or reduce it to a minimum, without increasing the risk of foetal anoxia.

3. To work out a practical and rapid way of deciding if the baby has lost blood to the extent that it requires a transfusion.

Incidence of the risk

During the period covered by the investigation, from January, 1951, to March, 1953, Caesarean section was performed 45 times in cases of placenta praevia, and the lower segment operation was used as a routine. In 20 of these placental tissue was found underlying the uterine incision to an extent which involved a risk of damage to the foetal circulation: that is to say, there was a 44 per cent chance of this complication being encountered.

Technique employed in lower segment operation

Macafee (1945) detailed the technique which he used in opening up the lower segment when the placenta lay anteriorly under the uterine incision. He stressed the importance of a stab incision and in one of his diagrams illustrated the point of the scalpel passing right down through the placenta into the amniotic cavity. Macafee did acknowledge that the umbilical cord was liable to be damaged during delivery when it was attached to the anterior portion of the placenta near the incision in the lower segment. We think that damage to vessels on the foetal aspect of the placenta may cause serious

blood loss from the foetal circulation. In our hospital attention is now paid to the steps employed at this critical phase in the operation and the following technique is employed in cases of placenta praevia.

A transverse incision no longer than 1 inch is made in the lower uterine segment. If the placenta is encountered the scalpel is immediately withdrawn and the incision extended on either side by means of fingers or blunt-pointed scissors. We know that it may be difficult to get into the correct layer at this stage but with experience we have found it possible to avoid gross disruption of the placenta. We then separate the placenta from its attachment by passing a hand upwards between uterus and placenta until the sac of membranes is reached. The membranes are ruptured by the fingers and the child's face delivered into the wound as quickly as possible. Once this has been done the umbilical cord is identified speedily and clamped. The remainder of the delivery takes place slowly and deliberately. The reason for delivering the child's face before clamping the cord is to reduce the chance of the child taking a breath *in utero*. In cases where foetal vessels in the placenta have been damaged, delay in clamping the cord may result in serious blood loss from the foetal circulation and by clamping the cord quickly the time available for blood to escape from the foetal circulation is reduced.

Assessment of the baby

Our emphasis on the need to work out a method of assessing whether these babies have lost sufficient blood to require a transfusion is explained by experiences which have convinced us that care and skill on the part of the surgeon cannot completely eliminate the risk of serious blood loss during a delivery of this kind: also, what is even more important, that clinical assessment of the baby alone is quite inadequate. In every case of placenta praevia the baby has been exposed to the risk of intra-uterine anoxia, and while it may sometimes be possible to distinguish the picture of restless pallor with respiratory distress of the purely anoxic baby from that of quiet, undistressed pallor seen in the exsanguinated baby, we have found it impossible to assess the situation rapidly and reliably, on the clinical picture alone, when confronted with a baby who may be suffering from a combination of the two. Moreover, we have found that the exsanguinated baby may appear deceptively well until shortly before death. The method of assessment which we have worked out for routine use depends on obtaining evidence from two sources.

First, by recording accurately the time which elapses after the placenta has been encountered until the cord is clamped, and by examining the placenta and membranes as soon as possible for evidence of damage to the foetal circulation, we try to gauge the risk of blood loss in that particular baby. The importance of the time-interval is self-evident, for it is a measure of the period during which the baby may be losing blood. Out of 12 cases in which this observation was made accurately, the interval was more than half a minute in 7, and as long as 3 minutes in 2 cases.

The subsequent examination of the placenta and membranes, for the purpose which we have in mind, is best carried out from the foetal aspect, for then the larger tributaries of the umbilical vein can be followed throughout their course and any damage to them noted. The results of such an examination are shown in Fig. 1, where one of these tributaries is seen to have been torn across at the edge of the hole through which the baby was delivered.

We now believe that if more than half a minute has elapsed between the placenta being encountered and the cord being clamped, or if there is visible damage to the foetal circulation, or both, there is a real risk that the baby has lost sufficient blood to need a transfusion. Of course, even in such a case blood loss may have been prevented by imponderable factors such as compression of the damaged vessel by the foetal parts (Case 18 in the Table and Fig. 2). But the value of this preliminary assessment in practice is borne out by the evidence from the second source.

This consists of serial estimation of the haemoglobin level in the baby's skin-prick blood. We are aware of the discrepancy which may be found between the haemoglobin levels in skin-prick and in venous blood during the first few days of life, the former tending to be on the average some

15 per cent higher than the true venous level. But we discovered by chance, early in the course of this investigation, that in these babies the haemoglobin level in skin-prick blood might fall well below the accepted normal range within as little as half an hour after blood loss had occurred. We thought that this observation might be the clue we were seeking, and our subsequent experience has convinced us that it is the answer to this part of the problem. The fact that skin-prick blood can be used is a great advantage in practice because, whether they have lost blood or not, these babies are liable to be very ill at the time when the serial haemoglobin estimations need to be made.

During the course of the investigation we felt it necessary to collect our own series of observations on the haemoglobin levels in normal babies during the first 24 hours of life, because the published evidence (summarized by Smith, 1951) showed big differences between different authors' findings. As a control we made 108 estimations in 34 babies during the first 24 hours of life, with the M.R.C. grey-wedge photometer (100 per cent=14·8 g. per 100 ml.). Skin-prick blood was obtained from the babies' heels, after warming if necessary. The controls, in none of whom was there any reason to believe that blood might have been lost, resembled the babies in whom we were interested in the following respects: in all 34 the cord was clamped immediately, or at most within half a minute after delivery; 28 of them were delivered by lower segment Caesarean section, and in 11 of these the indication for the operation was placenta praevia. Of the 108 estimations, 31 were made within the first 15 minutes of life; the remainder were scattered at random throughout the rest of the first 24 hours. The number of observations made in each baby varied between 1 and 8, and depended on a variety of circumstances, one of which was that we were trying to find the lower limit of the normal range, so that we tended to make more frequent estimations in those babies with the lowest haemoglobin levels.

The range of our results was 101-164 per cent (14·9-24·3 g. per 100 ml.), and we found that in any one baby there might be a considerable fluctuation, with a rise or fall of up to 20 per cent (3·0 g. per 100 ml.) during the first 24 hours. Because of the conscious bias in their collection, the results are not suitable for determining the full extent of the normal range, nor for ordinary statistical treatment. But our colleague Dr. E. G. Knox has analyzed them with full knowledge of the method of collection. He concludes that the probability of a normal baby's skin-prick haemoglobin level falling below 100 per cent (14·8 g.) within the first 24 hours is of the order of 1 in 40.

Comparable observations were made in 13 of the 20 babies whose placentae were encountered in the uterine incision, and whose clinical progress is briefly set out in the Table. The results of these observations, during the first 24 hours of life, are graphically represented in Fig. 2. Of these 13 babies, 4 were considered unlikely to have lost a significant amount of blood, judging by the speed with which the cord was clamped, and the appearence of the placenta (Cases 14, 15, 16 and 20). In all 4 the haemoglobin level stayed within the normal range. Of the 9 babies, in whom significant blood loss was considered

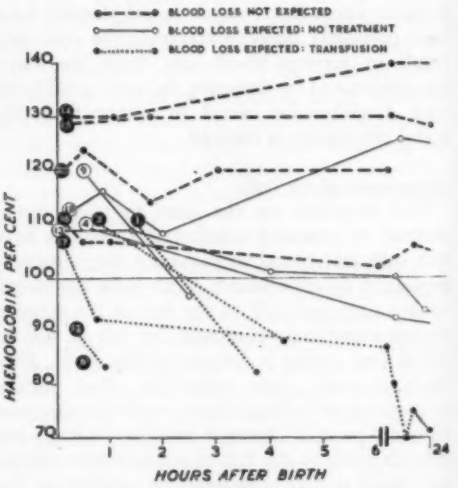

FIG. 2

Graphic representation of the haemoglobin estimations made during the first 24 hours of life in 13 of the 20 babies whose placentae were encountered by the uterine incision. Case numbers correspond with those in the Table.

likely to have occurred, 1 (Case 18) maintained haemoglobin levels within the normal range throughout the first 24 hours: 3 (Cases 4, 9 and 13) dropped to between 90 and 100 per cent (13·3 and 14·8 g. per 100 ml.), but did not require any treatment: and 5 (Cases 1, 3, 6, 12 and 17) fell to levels below 90 per cent (13·3 g. per 100 ml.) and were treated by blood transfusion. Their subsequent progress suggested that these transfusions had been necessary, and we now regard it as a fair assumption that, if haemolytic disease can be excluded, a baby whose skin-prick haemoglobin level falls to below 90 per cent (13·3 g. per 100 ml.) in the first 24 hours of life has lost blood to the extent that a transfusion should be given. If this indication arises within the first 3 hours of life, we regard the transfusion as a matter of urgency. It has been our practice to give these transfusions by polythene catheter through the umbilical vein; we run in 10 ml. of blood per pound of body weight rapidly, and then continue a slow drip until the baby's general condition is clinically satisfactory, or not improving with continued transfusion. In these very ill babies we have found it helpful to set up the transfusion in an Isolette incubator, working through the ports, so that the baby's oxygenation and temperature can be well maintained during the procedure.

A further 2 babies (Cases 10 and 11) received transfusions at the age of 30 minutes, without any indication from haemoglobin estimations. Both were considered likely to have lost blood: Case 10 was born at a time when we could not ensure adequate supervision during the next few hours, and the transfusion was regarded as a reasonable precaution; Case 11 appeared desperately ill, and responded well initially.

The following 2 brief case histories illustrate the points we want to make:

Case 6. This infant was delivered by the technique which we have recommended, but the cord had a velamentous insertion and, in rupturing the membranes with his fingers above the partially separated placenta, the operator tore across what amounted to vasa praevia, as was revealed by subsequent examination of the placenta and membranes. About 1 minute elapsed between this accident and the clamping of the cord. The baby was pale, but did not appear ill: his skin-prick haemoglobin level at 30 minutes was 84 per cent (12·4 g. per 100 ml.). An hour later he seemed rather cold and unresponsive, and it was decided that a blood transfusion was necessary; but the degree of urgency was not appreciated and time was wasted in cross-matching blood. By the time the transfusion was finally set up at the age of 3 hours the baby appeared moribund and died half an hour later. Autopsy revealed no cause of death except pallor of all organs.

Comment. This case occurred early in the series, before we had appreciated the urgent significance of such a haemoglobin level; it seems certain that the baby would have survived if the transfusion had been given within the first 2 hours of life. This case also illustrates the fact that, however much care is taken over the operation, serious damage to the foetal circulation cannot be completely eliminated as a risk in this type of delivery.

Case 12. The placenta was somewhat disrupted when being separated manually from the uterine wall, and 2½ minutes elapsed before the cord could be clamped. Subsequent examination showed that at least one major tributary of the umbilical vein had been torn across. The baby appeared to be ill and rather pale. The haemoglobin level at 20 minutes was 90 per cent (13·3 g. per 100 ml.) and by 55 minutes had fallen to 83 per cent (12·3 g. per 100 ml.). On this evidence a transfusion was rapidly set up in the incubator, and started at the age of 70 minutes. 100 ml. of blood (more than one-third of the baby's estimated blood volume) were transfused in the next 1½ hours. By the end of the transfusion the baby's condition was excellent, and it remained so thereafter. The haemoglobin level at the age of 42 hours was 112 per cent (16·6 g. per 100 ml.).

Comment. In this case the warning of the low (and rapidly falling) haemoglobin level was heeded, and the prompt action taken is regarded as having saved the baby's life.

Discussion

The numerical importance of this cause of neonatal death is difficult to assess: but it seems that the risk of it occurs about 10 times each year in this hospital. The value of the methods we have described, in terms of lives saved, cannot be tested statistically because of the small number of cases and the fact that the foetal and neonatal mortalities from placenta praevia result from a variety of causes, of which this is only one. Elimination of this cause could not be expected to show a statistically significant reduction of the mortality as a whole, especially as improvements in other directions are being attempted all the time. We do feel, however, that reliance on these methods has enabled us to approach the problem with a better understanding of the dangers involved, and to handle these dangers more confidently and promptly when

they do arise. We have also learnt something about the physiology of the newborn baby as shown by his prompt reaction to blood loss.

For many years it has been the practice of the medical staff in our hospital to perform the lower segment operation when Caesarean section is indicated in cases of placenta praevia, in the belief that this carries a lower risk for the mothers. We realize that this view is not held by all obstetricians. In a discussion of papers delivered to the Edinburgh Obstetrical Society (1947), Haultain, Lennie and Murray spoke in favour of the classical operation in cases of placenta praevia. Baird suggested that the question of upper or lower segment operation in placenta praevia was not of prime importance. Among those who prefer the lower segment operation are Macafee (1945), Marshall (1949) and Moir (1949). Those in favour of the classical operation believe that there is less risk of encountering the placental site and therefore less risk of heavy bleeding. Those who favour the lower segment section stress the smooth convalescence with less risk of complications in future pregnancies. These points refer to the mother and so far as we are aware no one has related the type of operation to the outlook for the baby, although Haultain (1947) suggested that the lower segment aproach might carry a greater risk for the child because of the possibility of the placenta being encountered. We cannot offer an opinion as to which of these operations carries the smaller risk for the baby as our experience has been limited to lower segment section in this type of case. In the lower segment operation we believe that the risk of foetal blood loss will be reduced to a minimum if the operator follows the technique which has been described in this paper.

In planning the management of the baby who has been exposed to the risk of blood loss from this cause, we have come to rely very greatly on the preliminary assessment of the magnitude of the risk in that particular case, by taking into consideration the time interval after encountering the placenta until the cord is clamped, together with the findings on subsequent examination of the placenta and membranes. If this assessment suggests that there is no risk of serious blood loss we are now content to forego the serial haemoglobin estimations. But if it suggests that a real risk exists, we consider it essential to obtain this evidence. We repeat the estimations more frequently if the haemoglobin level falls below 100 per cent (14·8 g. per 100 ml.), and give a blood transfusion if it falls below 90 per cent (13·3 g. per 100 ml.) within the first 24 hours of life.

We are well aware that the evidence on which this course of action is based falls short of what is desirable, and we regret having missed opportunities for obtaining relevant evidence in Cases 2, 5, 7, 8 and 11, especially as increasing skill in the delivery of these cases seems likely to reduce the supply of affected babies for further study. There are also theoretical objections to our interpretation of the fall in skin-prick haemoglobin levels as being evidence of rapid haemodilution in response to, and compensating for, rapid reduction in the baby's blood volume by blood loss. But there was nothing to suggest a haemolytic process in any of our cases: only 1 mother was Rhesus-negative, and the Coombs test on the baby's blood was negative (Case 17). The possibility that shock due to anoxia may produce peripheral vascular changes resulting in a fall in skin-prick haemoglobin levels receives no support from the fact that of the 11 control babies delivered by Caesarean section on account of placenta praevia several were very ill and 2 died, but none showed a comparable fall in haemoglobin level. It also seems possible that a baby whose initial haemoglobin level was high might experience a severe haemodilution without the level falling below 100 per cent (14·8 g. per 100 ml.). We have not encountered such a case in practice, but would regard with suspicion a fall of more than about 20 per cent (3·0 g. per 100 ml.) in the first few hours of life.

Our observations are consistent with those made in adults following blood loss resulting from venesection (Ebert, Stead and Gibson, 1941; Wallace and Sharpey-Schafer, 1941) or from limb wounds (Grant and Reeve, 1951), but it is our strong impression that haemodilution occurs more rapidly in these newborn babies. Several relevant observations in the newborn have been published since the start of our investigation. Busby and Neal (1951) reported a single case in which there was bleeding from a

TABLE

Details of 20 cases in which the Placenta was encountered during Lower Segment Caesarean section for Placenta Praevia

Case No.	Birth Weight	Damage to Foetal Circulation	Time until Cord Clamped	Lowest Haemoglobin Level	Transfusion	Comment
	lb. oz.			Per cent	ml.	
1	5 2½	Moderate	Long	82 at 3½ hr.	80 at 4½ hr.	Died at 11 hours. Autopsy showed massive bilateral suprarenal haemorrhage, with haematomata of liver and kidneys
2	6 7	Moderate	Not known	—	—	Satisfactory progress
3	7 5	Moderate	Not known	88 at 4½ hr.	75 at 7 hr.	Hb. 97 per cent at 25 hr. Satisfactory progress
4	6 4	Doubtful	1½ min.	91 at 49 hr.	—	Satisfactory progress
5	8 2	None	Doubtful	—	—	Satisfactory progress
6	4 14½	Severe	1 min.	84 at 30 min.	60 at 3 hr.	Died at 3½ hours. Autopsy showed pallor of all organs
7	5 2½	None	Short	—	—	Satisfactory progress
8	over 5 lb.	None	1 min.	—	—	Died at 26 hours. Autopsy showed atelectasis with extensive hyaline membranes in lungs
9	6 9	Moderate	Short	97 at 2½ hr.	—	Satisfactory progress
10	7 3	Moderate	3 min.	106 at 20 min.	70 at 30 min.	Transfusion given because adequate medical supervision could not be guaranteed. Hb. 120 per cent at 8 hours. Survived
11	3 11½	Moderate	3 min.	—	50 at 30 min.	Transfusion given because of placental findings and extreme pallor. Baby improved but died at 31 hours. Autopsy showed atelectasis with extensive hyaline membranes in lungs
12	6 15	Moderate	2½ min.	83 at 55 min.	100 at 70 min.	Hb. 112 per cent at 42 hours. Satisfactory progress
13	3 4	Moderate	½ min.	94 at 23 hr.	—	Hb. 97 per cent at 6 days, 60 per cent at 2 months: treated with iron. Satisfactory progress
14	4 15	None	½ min.	130 at 65 min.	—	Satisfactory progress
15	5 0	None	Short	107 at 38 hr.	—	Satisfactory progress
16	5 13	None	½ min.	102 at 6 hr.	—	Hb. 97 per cent at 43 hours. Satisfactory progress
17	8 0	Moderate	2 min.	58 at 33 hr.	80 at 39 hr.	Hb. 90 per cent at 57 hours: signs of circulatory overloading. Died at 19 days. Autopsy showed infantile type of coarctation of aorta
18	3 12	Slight	1½ min.	108 at 2 hr.	—	Hb. 60 per cent at 45 days. Satisfactory progress
19	6 3	None	Doubtful	128 at 25 min.	—	Satisfactory progress
20	6 6	None	½ min.	114 at 1½ hr.	—	Satisfactory progress

tributary of the umbilical vein during vaginal delivery, and the haemoglobin concentration in the baby's venous blood a short while later was 11·0 g. per 100 ml. Siddall and West (1952) reported 7 babies with abnormally low haemoglobin concentrations during the first day of life, in 6 of whom the presumed cause was blood loss resulting from incision of the placenta during Caesarean section. Wickster (1952) recommended repeated haemoglobin estimations in babies whose obstetric history suggests that blood may have been lost from the foetal circulation, but does not bring forward any direct evidence of their usefulness. We believe that the facts graphically represented in Fig. 2, and illustrated by the histories of Cases 6 and 12, support the adoption of the method as a routine procedure in the practical management of these cases.

Summary

1. In 45 consecutive cases of placenta praevia delivered by lower segment Caesarean section, the placenta was encountered in the uterine incision on 20 occasions. There is a risk of damage to the foetal circulation, with resultant blood loss of sufficient severity for a transfusion to be required, in all such cases.

2. By careful attention to the technique of delivery this risk can be reduced to a minimum. Details are described of an operative technique in which emphasis is placed on avoidance of damage to the placenta, and on rapid clamping of the cord after any risk of such damage.

3. In the management of the baby rapid assessment of the degree of blood loss is essential. One baby died at the age of 3½ hours because of delay in setting up a blood transfusion.

4. Clinical assessment of the baby alone has been found inadequate in these cases. We now assume that if more than half a minute has elapsed between encountering the placenta and clamping the cord, or if there is visible damage to the vessels when the placenta is examined from its foetal aspect there is a risk of serious blood loss in that baby. In such a case we have found serial estimation of the baby's skin-prick haemoglobin level a useful guide to the urgency of the situation. Observations in 13 of the 20 babies whose placentae were encountered, and in 34 control babies, have led us to believe that if the level falls below 100 per cent (14·8 g. per 100 ml.) within the first 24 hours of life, the baby has probably lost blood and requires to be watched with extra care: and that if it falls below 90 per cent (13·3 g. per 100 ml.) the baby requires a blood transfusion. If the fall occurs within the first 3 hours of life we regard the matter as one of urgency.

We wish to thank our colleagues on the obstetric staff who have allowed us to include in this report cases delivered by them, and Dr. L. M. Bruce and Dr. L. B. Strang, who made many of the observations on the babies; also Dr. E. G. Knox for his help with the statistical analysis of the control observations, and the Department of Photography, King's College, for Figs. 1 and 2.

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FIG. 1

The placenta in Case 13, from the foetal aspect, with the bag of membranes turned inside out. The strip of white cardboard forms a background for the tributary of the umbilical vein which was torn across at the edge of the hole through which the baby was delivered.

OLIGOSPERMIA AND PREGNANCY

A Study of 34 Cases

BY

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IT is commonly assumed that pregnancy brought about by semen of poor quality is more liable to result in an abnormal embryo and hence lead to abortion or the birth of a child with some congenital abnormality (Moench, 1933; Davidson, 1949; Walker, 1950; Royal Commission on Population, 1950). There is very little evidence to support this view and Snaith (1950) has suggested that the assumption is unwarranted and has emphasized that there is no conclusive evidence either way. One difficulty in deciding the point is the lack of agreement on what constitutes an abnormal seminal fluid. In the 34 cases described in this paper a low spermatozoon count has been taken as the criterion of poor quality semen; the counts ranged from 250,000 to 39,000,000 per c.cm. It is known that spermatozoon counts in this range are liable to be accompanied by other defects in semen quality (Macleod and Heim, 1945; Hammen, 1944; Hotchkiss and Macleod, 1946).

MATERIAL

The 34 couples, cases of primary infertility, had been investigated at subfertility clinics in Aberdeen or Newcastle-upon-Tyne and were traced during the course of a follow-up of patients who had attended these clinics. The period of infertility in 15 cases lay between 18 months and 3 years, in 16 cases between 3 years and 5 years, and in 3 cases was over 5 years. With few exceptions a pelvic examination, a tubal insufflation and a premenstrual curettage had been carried out on the women. Six of the women, at the time of conception, were under 25 years of age, 16 were between 26 and 30 years and 12 were over 30 years.

The majority of the husbands produced several semen specimens for analysis and the average spermatozoon counts are shown in Table I.

TABLE I

Spermatozoon Counts of the 34 Husbands

Spermatozoa per c.cm. (millions)	Number of Men
Below 1	5
1— 5	6
6—10	8
11—20	9
21—30	3
31—40	3

Outcome of the Pregnancies

Four of the pregnancies ended in abortion; 3 were unexplained and occurred before the end of the third month and 1 at 5 months was due to hydatidiform mole. Thirty of the pregnancies continued beyond the 28th week and in all of these cases live, healthy babies were born. All but 1 of the 30 mothers were delivered in maternity hospitals in Aberdeen or Newcastle-upon-Tyne; one patient was delivered at home and she gave full particulars of her pregnancy and labour and supplied photographs of the baby. There was no instance of congenital abnormality and the babies' weights ranged from 4 pounds 4 ounces to 9 pounds 4 ounces; 2 of the babies were under 5½ pounds. Eight of the women were delivered by forceps and the commonest reason for interference was delay in the second stage of labour. Caesarean section was performed in 2 cases because of disproportion.

Discussion

There are too few cases in this series for conclusions to be drawn but a study of the 34 cases produces no evidence to suggest that these pregnancies are more liable to be unsuccessful. Live, healthy babies were born in 30 of the cases and all but 2 were over 5½ pounds in weight. There were 4 abortions and this is not an unduly high proportion. Hignett (1953) has had experience of artificial insemination with poor quality semen in animals, and found that the pregnancies resulted in normal healthy young. Harvey and Jackson (1948a) have demonstrated, in vivo and in vitro, that abnormal spermatozoa rarely penetrate cervical mucus. Where semen quality is poor it is probable that the abnormal spermatozoa are less able to make progress in the female genital tract and a normal spermatozoon is more likely to reach and fertilize the ovum.

It has been suggested by certain authors (Zondek *et al.*, 1948; Tyler, 1951) that pregnancy does not occur when persistent, marked oligospermia is present. These authors suggest that pregnancy occurs only when oligospermia is periodic and alternates with occasions when the spermatozoon count approaches a normal level, but there is no doubt that this view is wrong. Harvey and Jackson (1948b) reported 7 cases where the husbands' counts were checked repeatedly and found to be below 20,000,000 per c.cm. and White and Barton (1951) reported 3 cases of pregnancy where the husbands' counts were below 1,000,000 per c.cm. on repeated examination. Included in the 34 cases described in this paper are 7 where the husbands' counts were checked repeatedly before and after conception and found to be below 10,000,000 per c.cm.; each resulted in the birth of a live, healthy child. The case of Mr. and Mrs. C. is an interesting example of persistent, marked oligospermia and pregnancy. The husband was first examined in 1944 and several semen analyses were made during 1944 and 1945; the count varied from 250,000 to 1,000,000 per c.cm. The number of abnormal spermatozoa was always over 25 per cent and the motility was poor. In 1946 the couple decided on adoption but they were keen to present the child as their own and Mrs. C. simulated pregnancy to the extent of wearing progressively larger cushions under her clothes and she arranged to go to another town "to have the baby in a nursing home". Within a few days of the adoption Mrs. C. conceived and further specimens of semen were obtained from her husband; the findings were the same as before. The couple's pleasure at the news of the pregnancy was overshadowed by some embarrassment at the thought of a conception so soon after the "birth" of the first child. This embarrassment was made all the more complete for the unfortunate couple when Mrs. C. went into premature labour and the child was delivered 8 months after the adoption of the first child. This was the first case encountered by the writer, where pregnancy occurred in spite of very poor quality semen and the possibility that Mr. C. was not the father of the child had to be kept in mind. Experience of a number of similar cases has since dispelled any doubts about the matter.

Summary

(1) It is commonly assumed that pregnancy brought about by semen of poor quality is more liable to be unsuccessful but there is little evidence to support this view.

(2) There is difficulty in deciding the point because of lack of agreement on what constitutes poor quality semen.

(3) In the 34 cases reported in this paper a low spermatozoon count has been taken as the criterion of poor quality semen; the husbands' counts ranged from 250,000 to 39,000,000 per c.cm.

(4) In 7 of the cases the husbands' spermatozoon counts were checked repeatedly before and after conception and found to be consistently below 10,000,000 per c.cm.; all 7 pregnancies continued successfully to term.

(5) Although the numbers are too small for conclusions to be drawn, a study of the end results in the 34 cases produces no evidence to suggest that these pregnancies are more liable to be unsuccessful.

I should like to thank Professor Evers for his encouragement and Mr. Linton Snaith for his kindness in allowing access to the records of his department in the Newcastle General Hospital.

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THE APPEARANCES OF LIPOID IN THE GENITAL TRACT OF THE MATURE VIRGIN GUINEA-PIG DURING THE OESTROUS CYCLE

BY

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THE present research was designed to study the distribution of lipoid in the epithelial lining of the uterine horns, uterine body, cervix and vagina of the guinea-pig during the oestrous cycle, and to relate the findings, if possible, to the activity of the ovarian hormones.

The lipoid appearances in the endometrium have already been studied in a number of animals and also in the human subject, and reference is made to these researches in the discussion in the present paper. The distribution of lipoid in the different parts of the uterus has, however, as far as we know, not been previously reported.

MATERIAL AND METHODS

Thirty-five virgin guinea-pigs aged about one year were used in the investigation and all were known to have a regular oestrous cycle, as verified by the vaginal smear technique (Stockard and Papanicolaou, 1917; Selle, 1922). Groups of animals were killed by chloroform on alternate days of the cycle and the whole uterus and vagina were removed.

Most of the specimens were fixed in 10 per cent formalin and frozen sections 10μ thick were made of the uterine horns, the upper and lower parts of the uterine body, the cervix and the vagina. The sections were stained with Sudan III for 15 minutes, then decolorized in 50 per cent alcohol and washed in distilled water. Haematin was used as a counter-stain. High concentrations of alcohol were avoided as these may dissolve some of the lipoid (Kaufmann and Lehmann, 1929; Romeis, 1929). Some of the specimens were fixed in Zenker-formol and stained with osmic acid using the technique described by Hoerr (1936).

ANATOMICAL NOTES

The following anatomical notes are considered necessary in relation to the text.

The two uterine horns join distally, but their lumina remain distinct for a considerable distance before uniting into a short, common cervical canal which in turn opens into the vagina. The body of the uterus, formed by the union of the two horns, may be described as consisting of a proximal part and a distal part. The measurements of the different parts of the uterus are shown in Fig. 1.

The uterine horns have a narrow slit-like lumen. The endometrium is lined by columnar or cubical epithelium and its stroma consists of an inner compact zone, the stratum compactum, and an outer looser zone, the stratum spongiosum. The uterine lumen is beset somewhat sparingly with the orifices of the uterine glands. The proximal portion of the uterine body is similar in structure to the horns.

In the distal part of the uterine body the endometrium becomes thrown into complicated villous-like processes, the glands are few in number and there is no evidence of division into the stratum compactum and stratum spongiosum. The upper part of the cervix is similar in structure to the distal part of the uterine body, and the lower part to the vagina.

RESULTS

Lipoid Appearances

These were found to vary in the different parts of the uterus, the cervix and the vagina at different periods of the cycle. The most prominent microscopical appearances are as follows:

Uterine Horns: The maximum appearances in

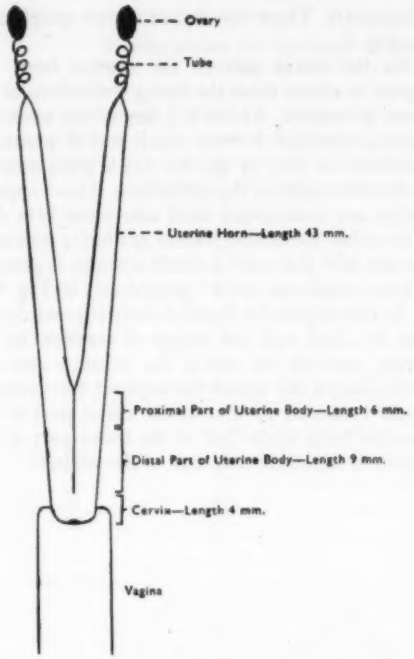

FIG. 1

Diagram of genital tract of guinea-pig showing the measurements of the different parts of the uterus.

the endometrium are seen at the 3rd and 9th days of the cycle. Fig. 2 shows the concentration of lipoid at the 3rd day. In the lining epithelium a considerable number of lipoid globules is present. They vary in size and in the first half of the cycle are more concentrated in the supranuclear part of the cells; thereafter they are distributed throughout the cells. The distribution of the lipoid around the uterine lumen is uneven, and there is no obvious concentration either at the mesometric or antimesometric side.

In the ducts of the glands the appearances generally follow those seen in the uterine epithelium, but the lipoid is slightly less in amount. The greatest amount is seen in the ducts at the 9th day of the cycle. In the gland-fundi only an occasional fat globule is seen in the lining cells at any stage of the cycle.

In the stroma of the endometrium a few large lipoid-containing cells are seen throughout the cycle. They tend to be rounded or irregular in shape and the lipoid globules are generally coarse, of varying size and mostly obscure the nucleus. They are found principally in the zone between the stratum compactum and stratum spongiosum and are most abundant at the 11th day of the cycle.

Proximal Part of Uterine Body: The appearances are identical with those seen in the uterine horns.

Distal Part of Uterine Body: The maximum lipoid appearances in the endometrium are present between the 7th and 11th days of the cycle. The epithelium covering the villous-like processes contains a great amount of lipoid (Fig. 3) and the distribution around the uterine lumen is fairly uniform. The lipoid globules are coarse and are mostly concentrated in the infranuclear zone of the cells. At the 11th day the globules are concentrated above and below the nucleus (Figs. 4 and 5). The cytoplasm adjoining the uterine lumen is practically always free of lipoid.

Cervix: The upper part of the cervix shows appearances similar to those found in the distal part of the uterine body. The lipoid appearances in the lower part of the cervix are similar to those found in the vagina. Fig. 6 shows the appearances in the lower part of the cervix at the 1st day of the cycle. The animal is in oestrus and the lining epithelium is stratified and contains many layers of cells. The innermost cells are being shed off into the lumen and contain coarse globules of lipoid distributed throughout the cytoplasm. Beneath these cells the epithelium is cornified. Lipoid is only present in the lower part of the cervix at oestrus.

Vagina: In the vaginal epithelium lipoid is only present at oestrus. The appearances at Stage I of oestrus are shown in Fig. 7. The superficial cells contain coarse droplets of lipoid and are in the process of being shed and can be stained in the cells of the vaginal smear (Nicol and Snell, 1954). The cornified cells at Stage II of oestrus show fine lipoid droplets which are mostly uniform in size and may obscure the nucleus. At Stage III, after the cornified cells are shed, the rounded epithelial cells show only a

small amount of fine lipoid droplets and in many of the cells lipoid is absent. No lipoid was noted in the epithelial cells at the 4th stage.

Amount and Distribution of Lipoid throughout the Cycle

This is shown for the different parts of the uterus, cervix and vagina in Table I. The differences in the amount of lipoid that did exist between the animals of the same group would seem to be accounted for by the natural differences among animals (Nicol, 1933).

In the uterine horns and proximal part of the uterine body lipoid is absent at oestrus. At the 3rd day of the cycle a small or moderate amount is present. Between the 5th and 7th days the lipoid has almost disappeared. At the 9th day a small or moderate amount is again present and falls rapidly to the 13th day, after which it disappears. These results are shown graphically in Fig. 8.

In the distal part of the uterine body the lipoid is absent from the lining epithelium at the time of oestrus. At the 3rd day of the cycle the amount present is very small but it gradually increases so that by the 9th day a great amount is seen throughout the epithelium. These appearances are maintained until about the 11th day. Thereafter the concentration gradually falls until at the 15th day only a small amount is present. These results are shown graphically in Fig. 9.

In the vagina the lipoid is only present during the 1st, 2nd and 3rd stages of oestrus. In the upper part of the cervix the amount and distribution of the lipoid throughout the oestrous cycle is similar to that in the distal part of the uterine body while that of the lower part of the cervix is identical with that of the vagina.

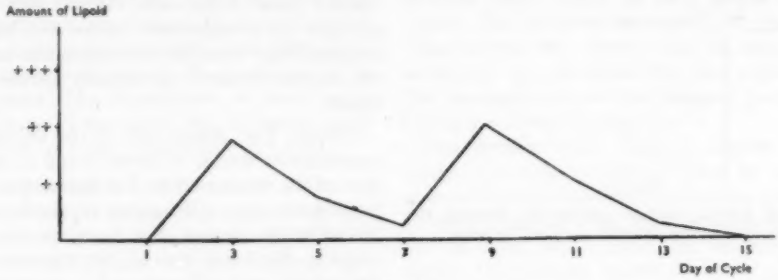

FIG. 8

Graph showing amount of lipoid in epithelium of uterine horn and proximal part of uterine body during the oestrous cycle in 35 guinea-pigs. The ordinates of the graph are the average amounts of lipoid in each group of animals for each day of the cycle.

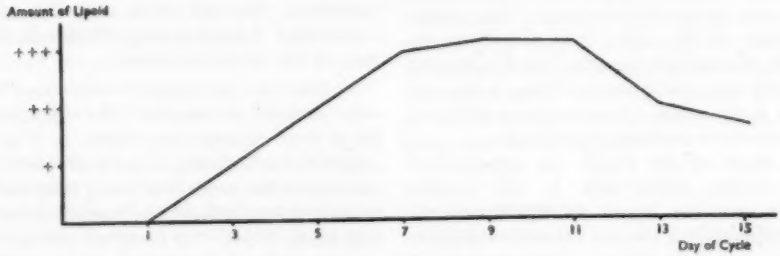

FIG. 9

Graph showing amount of lipoid in epithelium of distal part of uterine body during the oestrous cycle in 35 guinea-pigs. The ordinates of the graph are the average amounts of lipoid in each group of animals for each day of the cycle.

TABLE I

Showing amount and distribution of Lipoid in the Epithelium of the Uterus and Vagina during the Oestrous Cycle in 35 mature virgin Guinea-pigs

Day of cycle when killed	No. of animal	Uterine Horn	Proximal part of Uterine Body	Distal part of Uterine Body	Lower part of Cervix	Vagina
1st Day	68	—	—	—	++++	+++
	76	—	—	—	+++	+++
	7	—	—	—		++
	24	—	—	—		++
3rd Day	12	+	+	—		—
	1	++	++	+		
	4	+	+	+		—
	54	++	++	+	—	—
	64	+++	+++	++	—	—
5th Day	13	++	++	++		—
	33	—	+	++		—
	51	+	+	+++	—	—
	61	—	—	+	—	—
7th Day	14	—	—			—
	16	—	—			—
	63	—	—	++	+	—
	9	—	—	++++		—
	157	++	++	+++		—
9th Day	49	++	++	+++	—	—
	15	+++	++	++++		—
	18	+++	+++		—	—
	77	—	+	+++	—	—
	42	—	—			—
11th Day	57	+	+	++++	—	—
	25	+	+	+++	—	—
	28	+	+	+++	—	—
	20	—		++		—
13th Day	5	++	++	++++		—
	23	—	—			—
	50	—	—	+	—	—
	53	—	—	+	—	—
15th Day	27	—	—	++		—
	69	—	—	++	—	—
	26	—	—	+		—
	71	—	—	—	—	—

— = Absent.
\+ = Very small amount.
++ = Small amount.
+++ = Moderate amount.
++++ = Great amount.

Discussion

The distribution of lipoid in the human endometrium was first reported by Westphalen (1896), who described fine lipoid globules in the uterine glands of specimens from every phase of the menstrual cycle. Aschheim (1915) found fat in the uterine gland cells at the premenstrual phase of the cycle in about 80 per cent of human endometria examined. He considered that the increased concentration of lipoid indicates more intense cellular activity in preparation for nidation and that lipoids might constitute valuable foodstuffs and also be vehicles for vitamins.

Froboese (1924) found that fat was only present in the uterine gland cells of the human endometrium towards the end of the cycle when the endometrium showed evidence of commencing degeneration preceding menstruation, and that no epithelial fat was present in the middle of the second half of the cycle. He concluded that the fat in the uterine glands was evidence of cell degeneration.

Bourg (1929) found in the mouse that during dioestrus the cells of the uterine epithelium are filled with fatty globules which encircle the nucleus. During oestrus they disappear almost completely. At metoestrus they re-appear chiefly at the base of the cell. He implies that the uterine glands are to some small extent involved in this cycle. He also found that in the immature animal fatty globules appear in the uterine epithelium about the 6th day after birth and that by the 25th day the cells are filled with globules, and that the globules disappear after the administration of oestrogen.

Okey, Bloor and Corner (1930) chemically analyzed the uterine mucosa of the pig and found that both cholesterol and lecithin were present in increased amounts as the influence of the corpus luteum on the uterus developed.

Reese (1931), using a modified osmic acid technique, demonstrated a cyclic distribution of fat in the uterine epithelium of the rat. He found that the fat granules increase in size and number during metoestrus, reach their greatest abundance during the early interval and gradually diminish as dioestrus proceeds. He stated that the cyclic change does not appear to involve the glands.

Nicol (1935) reported for 10 guinea-pigs that there appears to be a cyclic distribution of fat both in the epithelium of the uterine horns and in the connective tissue of the endometrium and that the fat cycle corresponds with the period of activity of the corpus luteum. Further, in ovariectomized guinea-pigs, in which the uterus was previously sensitized by small doses of oestrogen, he showed that the corpus luteum hormone influenced the production of fat especially in the uterine epithelium. Fat was absent, or present only in very small amount, in the non-sensitized uterus.

Van Dyke and Chen (1940) analyzed the lipoid concentration of the endometrium at different stages of the cycle in the rhesus monkey and found that lipoid was increased in the luteal and menstrual phases.

Rossman (1941) also studied the cyclic changes of the endometrial lipoid of the rhesus monkey, using frozen sections. He found no pronounced cyclic changes in the lipoid of the surface epithelium. In the gland cells lipoid was present in maximum amount during the luteal and menstrual phases and practically absent during the follicular phase. The stromal cells in the superficial zone of the endometrium also showed a maximum amount of lipoid during the luteal phase. He related the lipoid appearances in the superficial part of the endometrium to the vascular supply of the endometrium described by Daron (1936) and Markee (1940) and concluded that the lipoid appearances were a form of fatty degeneration which occurred as a result of constriction of the blood vessels.

Gillman (1941) studied the distribution of lipoid in the human endometrium. He found that fat accumulated in the base of the gland-cells between the 19th and 25th days of the cycle, then rapidly disappeared so that by the 28th day only a few cells contained fat. During the first 3 weeks of the cycle fat was absent. He considered that the basal fat in the uterine gland-cells is not due to cell degeneration, but that it is a physiologically determined process regulated by the ovarian hormones and especially by the optimum metabolism of oestrogen and progesterone.

Gilbert (1942) carried out experimental work on castrated rabbits. She concluded that in relation to endometrial lipoid there is a delicate

balance between oestrogen and progesterone and that the optimum lipoid appearances are found only when the correct balance between these hormones exists.

Dawson and Kosters (1944) found in the cat that fat was absent from the endometrium during oestrus, but present on the 5th and 7th days after mating. The fat was limited in distribution, being restricted to the surface epithelium and that of the necks of the glands.

Alden (1947) found in the rat that lipoid was present in the uterine epithelium in small amount at oestrus. During early dioestrus lipoid droplets appeared in considerable numbers and were especially abundant during dioestrus. A progressive decrease then occurred towards the end of the cycle. The lipoid was largely confined to the surface epithelial cells and only rarely present in the cells of the glands. He also found that lipoid was present in the uterine epithelium before sexual maturity. In ovariectomized animals the lipoid gradually disappeared and by the end of the 4th week after operation only a few scattered droplets were present in the supranuclear zone of the cells.

Trilby (1943), Nicol and Snell (1954) described the lipoid appearances in the wall of the vagina and in the cells of the vaginal smear of the guinea-pig. These appearances were produced experimentally in ovariectomized animals by the administration of oestrogen (Nicol and Snell, 1954).

Previous researches therefore show that there is a cyclic distribution of lipoid in all mature uteri so far examined and that this appears to be related to the activity of the corpus luteum. In the human endometrium and in that of the rhesus monkey the lipoid is present chiefly in the glands, while in the mouse, rat, guinea-pig and cat it appears to be confined chiefly to the lining epithelium of the uterus.

The results of the present researches in the case of the uterine horns mostly agree with those previously reported for other animals. Lipoid is present in the cells of the lining epithelium for the greater part of dioestrus and reaches its maximum amount on the 3rd and 9th days. It is absent about the 7th day which coincides approximately with the time of implantation. The absence of lipoid about the 7th day is probably due to an alteration in the balance of action between oestrogen and progesterone since it has been shown by Bourg (1929) in the immature mouse that the administration of oestrogen reduces the lipoid content of the cells. Further, Gilbert (1942), working on the castrated rabbit, has shown that the maximum lipoid appearances are only present when the correct balance between oestrogen and progesterone is operating. It may be, however, that some other endocrine gland, such as the pituitary, is also involved in the control of this process, since the pituitary is known to possess an inherent cyclic activity (Smith and Engle, 1929; Wolfe, 1931; Wolfe, Cleveland and Campbell, 1932; Cleveland and Wolfe, 1933).

The exact role played by the lipoid in the epithelium of the uterine horns is difficult to explain. Rossman (1941) suggests that the lipoid appearances in the endometrium of the monkey are those of fatty degeneration possibly due to constriction of the blood vessels. Bacsich and Wyburn (1940) investigated the changes in the vascular architecture of the guinea-pig uterus during the oestrous cycle and found that during dioestrus there is a uniform vascular appearance throughout the uterus, but at oestrus the middle segment showed an antimesometric hyperaemia affecting particularly the stratum compactum. It was not possible to relate the present findings to these vascular changes. The microscopical appearances of the cells do not suggest those of fatty degeneration for the cell outline is normal and the nucleus has a healthy appearance. Further, fatty degeneration would not be expected to occur in the lining epithelium at this period of the cycle. For the above reasons it is suggested that the lipoid in the epithelium is an index of increased cellular metabolism possibly in preparation for the implantation and the subsequent nourishment of the ovum. This is in agreement with the views of Aschheim (1915). The fall in the amount of lipoid about the time of implantation may be due to a period of metabolic quiescence to allow the ovum to become properly embedded.

The lipoid appearances in the proximal part of the uterine body are similar to those in the uterine horns. This may be due to the fact that these parts are identical in structure. It should

be pointed out, however, that implantation does not occur normally in this part of the uterus.

In the distal part of the uterine body the lipoid appearances are more intense than in the other parts of the uterus. They reach a maximum about the 9th day of the cycle and this is more or less maintained until the 11th day. The duration corresponds approximately with the period of activity of the corpus luteum which is fully formed by the 5th day of the oestrous cycle (Loeb, 1906) and begins to regress about the 11th day or soon after (Loeb, 1911). As in the case of the uterine horns the microscopical appearances do not suggest those of fatty degeneration. The appearances again suggest increased cellular activity, but it is not possible to indicate the role played by the lipoid since this part of the uterus is a birth canal.

In the upper part of the cervix the lipoid appearances are similar to those in the distal part of the uterine body. This would be expected in view of their similar structure and function.

The above appearances in the uterine horns, proximal and distal parts of the uterine body were produced experimentally in double ovariectomized animals by the injection of progesterone preceded by a small sensitizing dose of oestrogen; these results will be reported in a subsequent paper.

The lipoid appearances of the lower part of the cervix and vagina are practically identical. Both parts are lined by stratified squamous epithelium and the presence of lipoid in the superficial cells, together with the unhealthy appearance of the nuclei, indicates that the cells undergo fatty degeneration prior to being cast off into the lumen. This process, in the case of the vagina, has been shown experimentally by Nicol and Snell (1954) to be under the control of oestrogen, and the lower end of the cervix is probably controlled in a similar manner.

Summary

(1) The presence of lipoid in the uterus and vagina has been studied in 35 mature virgin guinea-pigs during the oestrous cycle.

(2) In the uterine horns there is a cyclic distribution of lipoid in the lining epithelium. Its duration appears to correspond with the period of activity of the corpus luteum, but the lipoid is practically absent at the time of implantation. The most intense lipoid appearances in the uterus were seen in the distal part of the uterine body and also appear to be under luteal control. The lipoid appears to be an index of increased cellular metabolism.

(3) In contrast to the above appearances in the uterus lipoid only occurs in the epithelium of the lower cervix and vagina at oestrus and the appearances are those of fatty degeneration.

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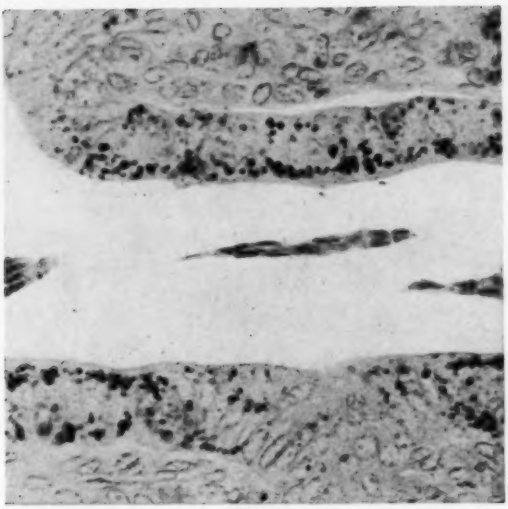

FIG. 2

Photomicrograph of section of uterine horn of virgin guinea-pig at 3rd day of cycle. The lining epithelium contains a considerable number of lipoid globules which vary in size and are most concentrated in the supranuclear zone of the cells. The lipoid appears black in the photomicrograph. Stained osmic acid. ×700.

FIG. 3

Photomicrograph of section of distal part of uterine body of virgin guinea-pig at 9th day of cycle. The epithelium covering the villous-like processes contains a great amount of lipoid and the distribution around the uterine lumen is fairly uniform. The lipoid globules appear black in the photomicrograph. Stained Sudan III and haematin. ×100.

FIG. 4

Photomicrograph of section of distal part of uterine body from virgin guinea-pig at 11th day of cycle. The epithelial cells contain a great amount of lipoid in the form of fine and coarse globules which are seen in the supranuclear and infranuclear zones of the cells. The lipoid appears black in the photomicrograph. Stained Sudan III and haematin. ×560.

FIG. 5

Higher magnification of section shown in Fig. 4. The epithelial cells have normal outlines and their nuclei appear healthy. They contain a great amount of lipoid in the form of fine and coarse globules which are seen in the supranuclear and infranuclear zones of the cells. The lipoid appears black in the photomicrograph. Stained Sudan III and haematin. ×820.

T.N., R.S.S.

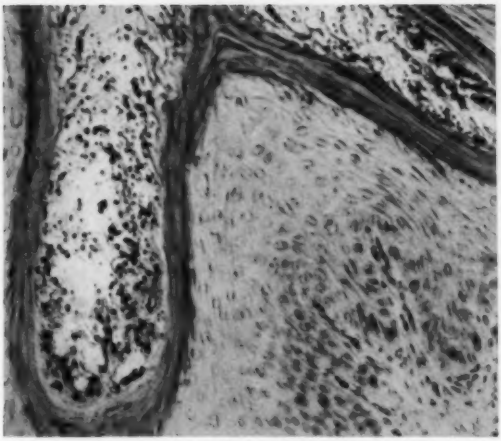

FIG. 6

Photomicrograph of section of lower part of cervix of virgin guinea-pig at Stage I of oestrus. The superficial epithelial cells contain coarse droplets of lipoid which appears black in the photomicrograph and some of the cells are being shed into the lumen. Stained Sudan III and haematin. ×200.

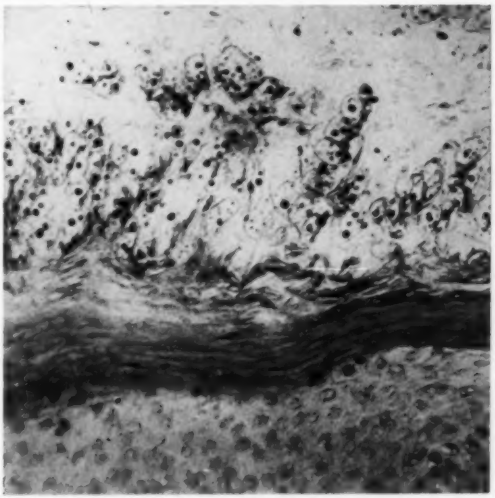

FIG. 7

Photomicrograph of section of vaginal wall of guinea-pig at Stage I of oestrus. The superficial epithelial cells contain coarse droplets of lipoid which appear black in the photomicrograph and some of the cells are being shed into the lumen. Stained Sudan III and haematin. ×300.

POSTERIOR PITUITARY SUBSTANCE IN THE URINE OF TOXAEMIC PATIENTS

A Preliminary Report

BY

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INTRODUCTION

THE presence or absence of antidiuretic and pressor substances in the blood and urine of eclamptic and pre-eclamptic patients has been the subject of much controversy which is still unsettled at the present time. Repeated claims have been made of discoveries of various substances with antidiuretic or pressor properties in the body fluids. One of the first of these claims was that made by Anselmino and Hoffmann (1931*a*, *b*, *c*) who reported the discovery of a substance resembling posterior pituitary extract in ultrafiltrates of blood from eclamptic and pre-eclamptic patients. This claim, however, was rebutted by de Wesselow and Griffiths (1934) and Hurwitz and Bullock (1935), although Mukherjee (1941), using methods similar to those of Anselmino and Hoffmann, has shown that the blood of severely toxaemic patients does contain a pressor substance.

Coester (1935) also claimed to have found an antidiuretic substance in the urine of toxaemic patients but this in turn has been denied by Byrom and Wilson (1934), Theobald (1934) and Levitt (1936). In 1939 Teel and Reid reported finding a urinary antidiuretic substance and claimed that it was of pituitary origin. Ham (1941) repeated this work and confirmed their findings but declared that the substance differed in some respects from posterior pituitary substance.

Krieger and Kilvington (1940) claimed that the antidiuretic factor could be extracted from urine of normal pregnant and even non-pregnant women as well as that of toxaemic patients. In 1946 they reviewed their work and claimed that significant amounts were only found in the urine from toxaemic patients, but the position was further confused by Krieger, Butler and Kilvington (1951) who reported that certain strains of *Bacterium coli* produce an antidiuretic substance. This led them to state that after due consideration they could not exclude the possibility that their previous results were due to bacterial contamination of the urine. They concluded that "it is unlikely that antidiuretic substances of pituitary origin can be regularly detected in the urine of toxaemic patients".

Meanwhile attention was directed towards the placenta as a possible source of antidiuretic and pressor factors in these patients and in 1942 Ham and Landis claimed to have detected the presence of these factors in saline extracts of that organ. This substance was said to be of colloid nature but was certainly not posterior pituitary extract substance. This work was repeated by Byrom (1951) but he was unable to find significant difference in the antidiuretic titre between pre-eclamptic and normal placentae and further suggested that the antidiuretic activity was largely, if not wholly, accounted for by bacterial contamination.

Despite this controversy and the failure to find specific factors responsible for oliguria and hypertension the search continues and a considerable body of opinion supports the idea of their existence. This idea has been sustained particularly in view of the repeated observation that toxaemic patients showed a marked sensitivity to posterior pituitary extract (Dieckmann and Michel, 1937; de Valera and Kellar, 1938), and this increased sensitivity has been variously attributed to the action of gonadotrophic hormones either of chorionic or pituitary origin

(Byrom, 1938; Browne, 1946; Govan and Mukherjee, 1950).

In addition the recent work on renal function and haemodynamic changes in pregnancy toxaemia indicates that these changes are functional and postulate some humoral mechanism (Kenny, Lawrence and Miller, 1950*a*, *b*).

The recent work of Arneil and Wilson (1953) on the wider field of oliguria related to renal disease in general is of considerable interest. Hitherto it has been considered that the oliguria frequently accompanying these diseases was due to organic changes in the renal parenchyma. This contention has not always been borne out by clinical experience and these authors claim to have isolated a polypeptide in the urine from patients suffering from a variety of renal conditions with the common factor of oliguria. This polypeptide is said to be similar in constitution to the antidiuretic principle of the posterior pituitary.

In view of the wide divergence of opinion which has been briefly reviewed above, it was decided to apply the methods of Arneil and Wilson to the investigation of toxaemic patients, and this paper is a preliminary report of the results obtained in a group of toxaemic pregnant women; normal pregnant women and non-pregnant women have been used to control the findings.

Materials

Where possible first morning specimens of urine were investigated. Non-catheter specimens were obtained from 18 patients exhibiting "hypertensive toxaemia of pregnancy", and 3 specimens from 2 cases of chronic nephritis in pregnancy. Four cases of eclampsia were studied. Catheter specimens were withdrawn as soon as possible after the occurrence of the first fit and, in addition, further catheter specimens were obtained at varying times thereafter.

The criteria of hypertension vary from author to author. In the present instance no case was included unless the systolic pressure was at least 140 mm. mercury and the lowest level of diastolic pressure accepted was 80 mm. mercury. In most cases there was an accompanying albuminuria and/or oedema.

Similar specimens were obtained from 14 normal pregnant women at varying stages in the later months of pregnancy and from 4 non-pregnant women in the reproductive period of life. These were considered to constitute an adequate control group.

For reasons which will be given later specimens of 4 preparations of commercial pituitary extract were also examined.

Methods

The specimens were examined within 6 hours of being voided and during the interval were stored in a refrigerator. This was taken to be important in view of the work of Krieger, Butler and Kilvington on bacterial contamination and antidiuretic activity.

A measured volume of urine was adjusted to approximately pH 5 with dilute acetic acid, B.D.H. wide range indicator paper being used, and was then immersed in a water bath and maintained at 100° C. for 10 minutes. This resulted in precipitation of the protein which after the urine had been allowed to cool was removed by filtering through No. 1 Whatmann's filter paper.

The volume of the filtrate was then restored to the original by the addition of sterile distilled water. Of the resulting filtrate 0·05 ml. was placed as a spot on a sheet of No. 1 Whatmann's filter paper, size 23½ by 18½ inches and run in chromatography tanks as described by Dent (1948) in an atmosphere of ammonia, the solvent being water-saturated liquefied phenol.

The paper was then dried in air, turned at right angles and run with butonal acetic acid* as the solvent. The method is illustrated diagrammatically in Fig. 1. After again drying in air the chromatogram was sprayed with a 0·1 w/v per cent solution of "Ninhydrin" in butonal. This was then left to develop and resulted in the appearance at various points on the paper of the purplish pink colour typical of the amino group. The polypeptide under investigation and various

* Butonal acetic acid is prepared by mixing 200 ml. A.R. butonal, 50 ml. A.R. acetic acid and 250 ml. distilled water in a separating funnel, allowing this mixture to equilibrate at room temperature and retaining for use the upper layer which forms in the separating funnel.

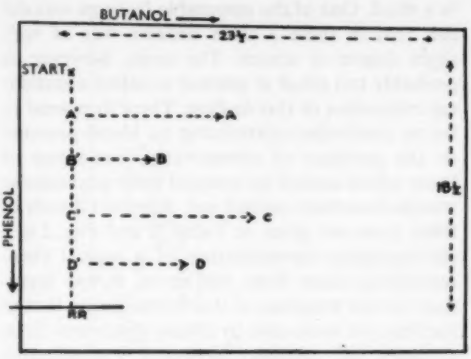

FIG. 1

Diagrammatic representation of a simple chromatogram containing four amino-acids A, B, C and D, and the "polypeptide" PP. A^1, B^1, C^1 and D^1 represent positions after linear separation in phenol and A, B, C and D the final position after treatment with butanol.

amino-acids could then be recognized by their typical positions on the paper, as compared with the chart prepared by Dent. The position of the various substances is related to their differential rates of flow in the two solvents. The first solvent produces a linear separation and treatment with butonal results in a two-dimensional chromatogram.

RESULTS

Control group

Development of the chromatograms of the control groups revealed certain variations in the amino-acid pattern. This was most noticeable when comparing the pregnant with the non-pregnant patients. Apart from these differences the main feature was the absence of the polypeptide described by Arneil and Wilson in all but 1 case. According to Arneil and Wilson this substance only moves in a linear direction under the influence of and at the same rate as phenol. It is not affected by butonal. It is therefore found constantly at the lowermost point of the phenol run. In 1 case only there was a slight suggestion of a substance possessing amino groups in this position. The staining reaction indicated that it was present in very low concentration (Table I, Case 13).

None of these patients showed any evidence of hypertension. A trace of oedema was present in

TABLE I

Normal Pregnancy

Case No.	Blood Pressure Mm. of Hg	Oedema	Albuminuria G./Litre	Maturity Weeks	Polypeptide	Reason for Admission
1	120/70	Nil	0	32	Negative	Pyelitis (post-treatment)
2	100/60	Nil	0	40+	Negative	Post-maturity
3	100/70	Nil	0	39	Negative	Contracted pelvis
4	110/70	Nil	0	36	Negative	Mitral stenosis—Gd. II
5	125/75	Nil	0	32	Negative	Anaemia
6	110/70	Nil	0	38	Negative	Rh. neg. with antibodies
7	125/75	Nil	0	40	Negative	Bad obstetric history
8	125/80	Nil	0	40	Negative	Bad obstetric history
9	110/65	Nil	0	34	Negative	Foetal abnormality
10	130/80	Trace	0	38	Negative	Breech presentation
11	115/70	Nil	0	33	Negative	Twin pregnancy
12	125/70	Trace	0	40	Negative	Contracted pelvis
13	120/70	Nil	0	40	Positive	Contracted pelvis
14	105/70	Nil	0	40	Negative	Contracted pelvis
		Normal Non-pregnant Women				
A	120/80	Nil	0	—	Negative	
B	110/70	Nil	0	—	Negative	
C	120/70	Nil	0	—	Negative	
D	115/70	Nil	0	—	Negative	

2 cases but this was unaccompanied by albuminuria. The urinary outputs were normal. No essential difference could be found between the patient whose urine gave a positive reaction for the polypeptide of Arneil and Wilson and those in whom the reaction was negative. Relevant details of these cases are given in Table I.

Hypertensive toxaemic group

The urines from 18 patients, diagnosed clinically as cases of "hypertensive toxaemia", were examined. All of these patients had a degree of hypertension varying from 140/80 to 210/135 mm. of mercury with a mean value of 156/98 mm. of mercury. All but 2 were oedematous. In 3 instances the oedema was very slight. It was generalized in 1 case and in 8 it was of major degree. Albuminuria, up to 7 parts Esbach, was present in 14 of the cases. Examination of the chromatograms of the urine from these patients revealed the certain presence of Arneil and Wilson's polypeptide in 15 cases. It was absent in 2 instances and doubtfully present in a third. One of the noticeable features was the fact that in these 3 cases oedema was of very slight degree or absent. The series, however, is probably too small at present to allow a statistical evaluation of this finding. There appeared to be no particular relationship to blood-pressure or the presence of albuminuria, but many of these points cannot be assessed until quantitative studies have been carried out. Relevant details of these cases are given in Table II and Fig. 2 is a photographic representation of a typical chromatogram taken from this series. It was fortunate for the purposes of this investigation that at the time we were able to obtain specimens from 2 cases of chronic nephritis complicating pregnancy. Both of these patients were seen early in pregnancy and found to have a gross degree of hypertension. In addition, there was a history of acute nephritis in early life and examination of the urine together with renal function tests confirmed the diagnosis. There was a moderate degree of oedema in 1 case and both had albuminuria.

TABLE II

Hypertensive Toxaemia of Pregnancy

Case No.	Blood pressure Mm. of Hg	Oedema	Albuminuria G./Litre	Maturity Weeks	Remarks	Polypeptide
1	140/80	+	½	38		Positive
2	140/80	++	½	39		Positive
3	140/90	++	0	39		Positive
4	150/100	++	3	32		Positive
5	150/90	+	1½	33		Positive
6	145/95	++	1½	40		Positive
7	160/105	+	7	40		Positive
8	140/100	++	1	36		Positive
9	210/135	+++	3	33		Positive
10	170/100	+	½	40	Very slight oedema	Negative
11	170/100	Nil	0	30+		Positive
12	155/95	++	3	37		Positive
13	150/100	++	0	38		Positive
14	160/110	+	0	39		Positive
15	150/105	+	1	36	Very slight oedema	Negative
16	165/100	++	2	38		Positive
17	165/90	Nil	1	37	No oedema	Doubtful
18	150/100	+	1½	38		Positive
19	180/105	+	1	26	Chronic nephritis	Positive
20	205/135	Nil	2	16	Chronic nephritis	Doubtful
21	210/140	Nil	3	17	Chronic nephritis. No oedema	Positive

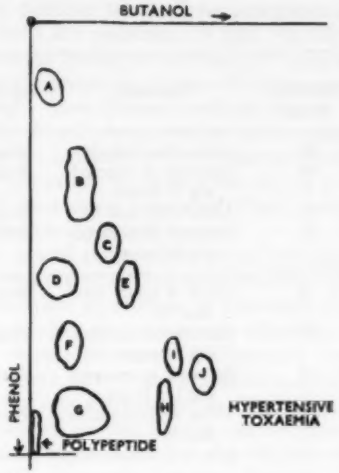

FIG. 2

Typical chromatogram from case of "Hypertensive Toxaemia". A-J represent various amino-acids.

The presence of the polypeptide was easily detected in 1 case, that showing oedema, but the specimen from the other patient gave a very doubtful result. On repeating the run with a further specimen a definite positive was obtained. Some details of these 2 cases are included in Table II.

Eclamptic group

Specimens of urine, 8 in all, from 4 cases of eclampsia were also examined. The urine was obtained as soon as possible after the first fit and in 2 cases the specimen was obtained by catheter immediately after cessation of the seizure. In the other 2 cases examination was delayed owing to a period of anuria for several hours following the convulsion. Further catheter specimens were withdrawn from 3 of the patients while the convulsive stage continued. In 1 case this stage lasted for at least 49 hours. Every case showed marked hypertension with generalized oedema and a gross degree of albuminuria. The number of fits varied from 1 in Case 2 to 7 in Case 3.

All specimens so far examined have given a positive reaction for the "polypeptide". It is impossible to state at present whether this substance persists in the urine for a prolonged period, but so far it has been detected up to 49 hours after the first fit. This patient, however, was still in the eclamptic phase and further study will be necessary before one can state whether the substance continues to be excreted after the cessation of fits. Rough comparison of the results with those obtained in the "hypertensive toxaemic" group tends to indicate that the substance is present in greater concentration in the eclamptic patient but this may be due in part to the highly concentrated urine excreted by these patients. The relevant findings in this group are shown in Table III and a typical chromatogram is illustrated in Fig. 4.

According to Arneil and Wilson the polypeptide present in the urine from their cases of renal disease was found in a position on the chromatogram identical with that occupied by a similar compound detected by them in commercial extracts of posterior pituitary gland. Analysis of the amino-acid structure indicated that the substances were of similar nature. The fact that a substance possessing amino groups has been found in a similar situation on the chromatograms of the urine from "toxaemic" and eclamptic patients is presumptive evidence that the urine of these patients contains a compound similar in structure to posterior pituitary extract. Nevertheless, it was considered advisable to apply our methods to commercial extracts to confirm this point. Consequently 4 such extracts prepared by different manufacturers were studied. All were found to give very similar chromatograms and all contained a substance which ran in phenol and remained stationary in butonal. Fig. 4 is a photograph of the chromatogram provided by one of these preparations. It will be seen from this that a considerable quantity of material is found at the end of the phenol run, occupying the same position as the substance found in the urine of our patients and as the polypeptide described by Arneil and Wilson.

DISCUSSION

As this paper is in the nature of a preliminary report it is felt that discussion of the findings should largely be reserved until the source, nature and pharmacological properties of the

TABLE III
Eclampsia

Case No.	Blood Pressure Mm. of Hg	Oedema	Albuminuria G./Litre	No. of fits	Maturity Weeks	Remarks	Polypeptide
1	190/100	+++	12	3	40	Urine after first fit	Positive
	190/100	+++	12		40	Secreted in succeeding 10 hours	Positive
2	170/90	+++	8	1	38	Urine after first fit	Positive
	170/90	+++	8		38	Secreted in succeeding 14 hours	Positive
3	180/100	+++	+++	7	38	Urine 9 hours after first fit	Positive
	180/100	+++	14		38	Secreted in succeeding 24 hours	Positive
	150/100	+++	2¼		38	Secreted in succeeding 15¾ hours	Positive
4	180/85	+++	14	2	40	Urine 4½ hours after first fit	Positive

"polypeptide" have been more fully investigated. However, two points seem at the present time worthy of some comment.

The first is the quantity of urine, 0·05 ml., selected for investigation. This amount was chosen since experience has shown that when larger amounts are used the sodium chloride and other salts present in the urine interfere with the satisfactory running of the chromatogram. This limitation may have proved fortunate in the present instance, as in the majority of cases of "hypertensive toxaemia" and in all cases of eclampsia so far investigated a positive result has been obtained with this quantity of urine. This is in contrast to the specimens from normal pregnant and non-pregnant patients where only 1

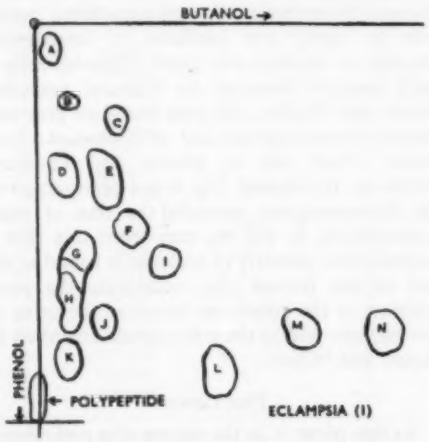

FIG. 3
Typical chromatogram from a case of Eclampsia. A-N represent various amino-acids.

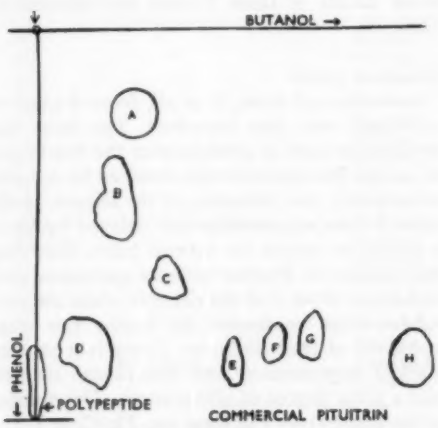

FIG. 4
Typical chromatogram from commercial posterior pituitary extract. A-H represent various amino-acids.

gave a positive result. Two interpretations of these facts are possible; (1) that the difference between the findings in normal and "hypertensive toxaemic" pregnancy is one of degree and that all might have proved positive had a larger quantity of urine been selected for investigation; (2) that the isolated positive result in the normal series may either be in error or may be an early sign of an ensuing toxaemia. These points will need further investigation.

The second point arises out of the considerable literature which has accumulated regarding the causation of oliguria in toxaemia of pregnancy. Despite the controversy which has arisen since Anselmino and Hoffmann's original report there have been a sufficient number of reports of a positive nature to suggest that some substance of an antidiuretic nature does exist. No other explanation for the oliguria of pre-eclamptic toxaemia seems feasible. There appears to be insufficient anatomical change in the renal parenchyma to account for this oliguria and the rapid return to normal after delivery indicates that the oliguria cannot be due to organic changes but is of functional nature. Renal function tests confirm this impression and further suggest that some humoral agent may be responsible. A possible explanation for the varying results obtained by different observers may lie in the criteria adopted in the selection of cases for investigation. Many observers have relied entirely upon hypertension as the diagnostic indication of pre-eclamptic toxaemia. Other writers have shown, however, that various forms of hypertension may be met with in the pregnant patient, not all of them associated with toxaemia. In any attempt that may be made to detect antidiuretic substances it seems only logical to relate their possible presence to the occurrence of oliguria and oedema. This may indeed account for the contradictory reports in the past. It has been shown in the present series that the "polypeptide" is apparently related to the presence of oedema. Arneil and Wilson have claimed that the substance detected in their cases possesses antidiuretic properties. Further work is at present in progress to determine the pharmacological nature of the very similar material found in the present series of cases.

Summary

1. Urines from cases of eclampsia, hypertensive toxaemia and chronic nephritis in pregnancy, and from normal pregnant and non-pregnant women were subjected to analysis by paper chromatography.

2. In all cases of eclampsia and in the majority of cases of hypertension complicating pregnancy a substance has been found which moves with phenol but remains stationary when treated with butanol. Only 1 normal urine contained this substance.

3. This constituent of the urine is found in a position on the chromatogram identical with that occupied by the antidiuretic polypeptide described by Arneil and Wilson. The same position is taken up by a polypeptide in posterior pituitary extract.

4. The presence of the substance appears to be related to the presence of oedema.

Acknowledgments

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ELECTROCARDIOGRAPHY AND PHONOCARDIOGRAPHY OF THE FOETAL HEART

BY

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HISTORY

GENERAL interest in obtaining accurate and precise information with regard to the foetal heart by electrocardiographic means dates back to 1906, when Cremer (1906) obtained two tiny tracings, apparently due to foetal deflections, whilst recording the electrocardiogram of a pregnant woman at term.

Further attempts to develop foetal electrocardiography in the next twenty years were largely unsuccessful because of technical difficulties. Foa (1911) and Krumbhaar (1916) each recorded a single successful case, whereas Sachs (1922) and Haynal and Kellner (1924) made a comprehensive study with the apparatus then available using abdomino-vaginal and rectal leads, but failed to identify definite foetal deflections.

Little more was added to the subject until about 1930, when the rapid development of electrical amplification permitted the graphic recording of much smaller currents than was possible with the string galvanometer alone. Maekawa and Toyoshima (1930) designed a valve amplifier which they used in conjunction with a galvanometer to record clear deflections of foetal origin from the abdominal leads of a woman in labour.

These early and somewhat scattered observations served, at least, to focus attention on the possibilities of foetal heart electrocardiography for practical application.

The amplifier electrocardiogram had, to some extent, succeeded in overcoming the outside interference which had disturbed the earlier workers and a series of amplification sensitivities could be utilized to standardize the recordings. Steffan and Strassmann (1933) obtained positive results in a small series, and Easby (1934) reported a positive foetal electrocardiogram on a 4½-months' foetus removed from the uterus by hysterotomy. Strassmann and Mussey (1938), using a 5-lead technique, obtained positive foetal electrocardiograms in 87 per cent of 52 gravidae.

It was in 1938 that Bell, in one of the few papers to come from the United Kingdom on this subject, reported a new and more successful approach, using an amplifier thermionic valve electrocardiograph with a balanced input system. He obtained foetal deflections of several millimetres amplitude and recorded the first double set of foetal wave tracings in a case of multiple pregnancy. Bell (1938), in his discussion of foetal electrocardiography, presented arguments to show that foetal deflections can be best identified by the simultaneous recording of foetal potential changes and heart sounds. Attempts at recording the intra-uterine heart sounds had been made as early as 1908 by Hofbauer and Weiss and a few photographic recordings were obtained by Beruti (1923). Phonograph disc records of the foetal heart had been made by Lian, Goldbin and Minot (1938) and good recordings were obtained on 52 successive cases made on discs by Smith and Hervert (1940). Smith (1941) obtained a disc record of foetal hearts in a case of twin pregnancy in which there was a question of the viability of the infants. He was able to confirm, by this means, a diagnosis of live twins.

Dressler and Moskowitz (1941) made the first attempt to study the foetal heart sounds and electrocardiograms simultaneously. The purpose of their study was "to develop a positive method by means of which to determine in pregnancy and labour, whether the foetus was alive or not". These workers studied 40 gravid women, all of

whom gave birth to live babies. The heart sound recordings were positive in 100 per cent. The foetal electrocardiogram tracings were obtained with certainty in 80 per cent.

Mann and Bernstein (1941) obtained 90 per cent positive tracings in a series of 40 pregnancies and concluded that, in some cases, foetal distress and death in utero can be definitely diagnosed. The earliest clearly defined foetal deflection was obtained on the 169th day before term.

The work of Goodyer, Geiger and Munro (1942) at Yale marked a real advance in foetal electrocardiography. These workers obtained records in which the foetal Q.R.S. complexes measured 10-14 mm. and thus clearly indicated that exact information about the foetal heart was within reach.

After 20 years of relatively little advance, some progress was made in several directions. The phonocardiograph as well as the electroencephalograph were used in the investigation of the foetal heart. Ward and Kennedy (1942), using a 3-channel electroencephalograph, obtained 82 per cent positive tracings from the 17th week of pregnancy onwards. Paley and Krell (1944) published a series of combined foetal electrocardiograms and stethograms, in which they reported 79 per cent successful tracings.

Blondheim (1947) presented the second series of cases in which the electroencephalograph, without modification, was used. In this series 82 per cent were positive tracings. It is doubtful if the electroencephalograph possesses any real advantage in these studies. Blondheim obtained foetal heart amplitudes of 8 mm. and these can be bettered by standard electrocardiography. This is fortunate, for if foetal electrocardiography is to be of use to the clinician, a simple and easily applied technique must be available.

Smyth (1953) has reported a series of electrocardiographic recordings in which 100 patients were investigated. He reports that the foetal Q.R.S. complex was recognized in all but 2 and in these 2 cases the foetus was dead. Smyth has improved the method by the addition of an iso-electric belt, thus eliminating maternal heartbeat potentials from the foetal recording.

In a recent demonstration before the Obstetric Section of the Royal Society of Medicine, London, Gunn and Wood (1953) showed an apparatus for foetal heart sound recording, using a high gain amplifier to detect signals of less than 100 microvolts.

The effects of external cephalic version and head pressure upon the foetal heart sounds were heard with the utmost clarity and clearly recorded.

Apparatus

The instrument used in this study was the portable electrocardiograph (Elmqvist) in conjunction with a single stage resistance-coupled valve pre-amplifier of simple design. (The instrument was constructed by General Radiological Ltd., London.) The unit, employing a photographic method of recording, is fairly impervious to mechanical interference and shock. Battery operation eliminates such heavy components as transformers and choke coils and reduces the possibility of mains interference, as well as enabling light-weight construction.

The phonocardiographic unit comprises a separate amplifier specially designed to handle audio frequencies and is equipped with mains control. A special crystal microphone is used which is protected by a rubber moulding, designed to prevent interference from extraneous sources. The filter control provides frequency coverage in 5 steps up to 750 cycles per second. The heart sound recorder is used in conjunction with the electrocardiograph, to which an extra galvanometer, for its reception, is fitted. The pre-amplifier circuit increases the over-all sensitivity of the recording apparatus approximately 20-30 fold. Various degrees of sensitivity are available.

The electrocardiograph was adjusted to normal or double standardization (1-2 cm. per millivolt), as advocated by Mann and Bernstein (1941), and this was found adequate for foetal heart recording. A condenser was used to eliminate baseline tremor.

Method

The patient is arranged in a reclining position on a comfortable couch, with shoulders and head slightly raised. A short period of rest before starting recording was found to be useful for inducing mental and physical relaxation, thus

reducing baseline disturbances. The recordings were made in a room selected to avoid outside noise and electrical apparatus, which might interfere with the clarity of the tracings. It was found to be important that the bladder and bowel be empty.

The selection of leads and the exact placing of electrodes is of the utmost importance for the clarification of foetal deflections. Early investigators used rectal and vaginal leads with little success: this was followed by the use of the standard limb leads taken from the proximal parts of the limbs. Leads taken directly from the maternal abdomen give foetal deflections of larger amplitudes so allowing a better recording.

Welsh self-retaining suction electrodes, well prepared with "electrode jelly", were found to give maximum contact over an area nearly twice that covered by the flat chest electrode. Numerous abdominal lead positions have been used to establish the optimum electrode placing. Goodyer, Geiger and Munro (1942) experimented with 17 varieties of electrode positions and found that the greatest number of positive recordings were obtained in the following leads: (1) epigastric-suprapubic (114), (2) right upper uterine quadrant to left lower quadrant (105), (3) right lower uterine quadrant to left upper quadrant (102). A third electrode was placed on the left upper thigh to reduce interference pick-up. The use of the diagonal leads from the upper quadrants to the opposite lower quadrants increases the angle between the leads and so increases the likelihood of picking up weaker potentials from near longitudinal lies of the foetal heart. The upper electrode was placed at the upper limit of the uterine fundus in the midline, as determined by palpation. After numerous trials it was found that, in all instances, the epigastric-suprapubic lead gave a positive tracing when such a tracing was obtained by any other lead.

Lindsley (1942) has shown that the deflections due to the maternal heart can be eliminated by varying the position of the electrodes; as the upper electrode is brought down over the uterus closer to the suprapubic electrode, so the maternal deflections diminish.

The explanation is probably that this is due to a large potential drop in a relatively short distance. There is little advantage to be gained by this method of elimination of maternal complexes, since their presence helps in the timing and identification of the foetal deflections.

Table I shows the percentage positive results with the various leads in this study. Lead 1 (epigastric-suprapubic) was found to give best results and was used routinely in the present study.

TABLE I

Percentage of Positive Tracings with Various Leads

Leads	Percentage Positive
Lead 1. Epigastric-suprapubic	92
Lead 2. Right upper quadrant to left lower quadrant	87
Lead 3. Right lower quadrant to left upper quadrant	85
Transverse umbilical leads	50

The phonocardiographic recordings were obtained by the following technique. The microphone was placed lightly on the maternal abdomen and the maximum foetal heart sounds located by gently "seeking" the abdomen. The maximum sounds were clarified by means of the volume control, "listening-in" directly with the amplified stethoscope fitted to the unit. The recording light-spot on a calibrated red screen was adjusted by means of a sensitivity control on the panel. If no heart sounds were detected, after a careful search of all quadrants, a trial tracing was recorded from each quadrant. By this means heart sounds were recorded in several cases when direct listening did not help in detection. Having completed all connections the foetal heart electrocardiogram and phonocardiogram were recorded simultaneously. The film speed was 25-50 mm. per second. Two feet of film were used in each recording to facilitate close study of the tracings.

There are many factors that influence the success of the recordings. Amongst these are: (1) the thickness of the abdominal wall, (2) the interposition of the placenta, (3) the somatic muscle tremor and electrical potentials of the muscle, (4) the amount of amniotic fluid, (5) poor electrical contact, (6) outside electrical interference, (7) foetal and uterine movement, and (8) maternal bowel sounds.

The influence of the thickness of the maternal abdominal wall in preventing adequate auscultation of the foetal heart by ordinary means is well known. Foetal electrocardiograms taken directly from the unopened uterus at Caesarean section (4 cases) were of considerably greater amplitude than those obtained from the same patients just prior to operation, confirming the work of Mann and Mayer (1942). The direct effect of the amniotic fluid is less of a barrier to sound conduction and potential recording than are the fat and muscle of the abdominal wall.

Results

One hundred and ninety electrocardiographic and phonocardiographic recordings were made upon two groups of patients.

Group 1 consisted of 110 unselected cases, approximately half of whom were primigravidae. All recordings in this group were upon patients near or at term. The subjects ranged from 18 to 46 years of age and all body types were included without discrimination. Positive results, confirmed by delivery of living infants, were 98 per cent.

Group 2 consisted of 80 cases selected because of obstetric interest, many in a relatively early stage of pregnancy, in an attempt to obtain the foetal recordings as early in pregnancy as possible. The earliest foetal electrocardiogram was obtained at the 17th week of pregnancy and the earliest heart sound recording to be clearly identified was at the 15th week.

In the total series (Groups 1 and 2) of 190 records from the 15th week of pregnancy to term, 163 or 85·8 per cent showed positive foetal deflections and heart sounds.

Clinical Applications

It was intended, in this work, to study problems of direct application to day-to-day obstetrics by means of foetal recordings.

1. *The diagnosis of foetal intra-uterine life and death*

The diagnosis of foetal intra-uterine life, when foetal movements are in doubt and the heart sounds inaudible on simple auscultation, may present clinical difficulty. The presence of a positive foetal heart recording supported by a simultaneous sound tracing means that the foetus is alive, whereas its absence does not necessarily signify foetal death, although these findings may help in assessment.

A positive electrocardiographic result, in this respect, is of more immediate significance than a positive laboratory pregnancy test, for the latter depending on the presence of chorionic tissue may remain positive for a week or two after the intra-uterine death of the foetus. An undisputed advantage may be gained by the use of the foetal electrocardiogram in a suspected case of hydatidiform mole when the biological test remains positive. By the same token the electrocardiograph has proved of value in differentiating between pregnancy and other abdominal tumours simulating cyesis. In this series, 8 cases in which there were good grounds for the clinical suspicion of foetal death were studied. Six negative tracings were obtained and in all these cases intra-uterine death was confirmed at subsequent delivery. Two positive tracings confirmed living infants.

Illustrative problems

1. *Case 37.* An anxious primigravida aged 39 years at term was admitted with moderate pregnancy toxaemia. She had not felt any foetal movements for several days. The heart sounds were inaudible on simple auscultation. Foetal deflections and heart sounds were obtained and the patient reassured. A living infant was obtained by vaginal delivery.

2. *Case 102.* A multipara at the 30th week of pregnancy gave a history of intermittent vaginal bleeding for 2 weeks. Foetal movements had not been felt with any certainty, but the mother was unsure of this. The electrocardiogram showed no foetal deflections and labour was induced. A macerated still-born infant was delivered.

3. *Case 32.* A diagnosis of uterine fibroids had been made in a woman of 32 years. There was no history of amenorrhoea, but there had been a relatively rapid enlargement of the uterus. Foetal electrocardiography confirmed that a 25-week pregnancy was complicated by uterine fibroids.

2. *Multiple pregnancy and breech presentations*

The use of electrocardiography in the diagnosis of multiple pregnancy by the demonstration of 2 distinct sets of foetal deflections has been discussed by Goodyer, Geiger and Munro (1942). Theoretically, multiple pregnancies may be diagnosed from the 17th week of pregnancy onwards by this method, somewhat earlier than is now possible by auscultation or roentgenography, but the possibility of overlooking the double deflections is high and, at the present time, does not offer any definite advantages, although perfection of the technique may help to solve this problem. Dressler and Moskowitz (1941) were able to disprove 2 suspected cases of multiple pregnancy by electrocardiography. Bell (1938) made an early clear recording of twin foetal hearts.

Breech presentation can be confirmed by the fact that the axis of foetal deflections in breech presentations is in the same direction as the maternal heart deflection. From the 28th week of pregnancy onwards 5 cases of breech presentation showed upright or occasional diaphasic deflections which reverted to a downward type after external cephalic version had been performed.

3. *The evaluation of alterations of the foetal heart deflections and sounds during prolonged labour.* (*Foetal stress and distress.*)

Smyth (1953) has pointed out that "in recent years regard to the importance of early recognition of signs of foetal distress has led to some reduction of the still-birth rate—if further improvement is to be obtained, then a more reliable method than occasional listening to the foetal heart is necessary for the recognition of foetal distress."

In order to determine whether a foetal electrocardiogram is positive the following criteria, suggested by Dressler and Moskowitz, have been followed: (1) the R wave must be followed throughout the entire lead, (2) it must occur at more or less regular time intervals, (3) the interval must correspond in length to the distance between each foetal heart sound as recorded by the phonocardiograph (allowing for the normal small time lag), and (4) the foetal heart rate, as recorded by the distance between 2 foetal heart deflections, must correspond to the rate as determined by the phonocardiograph. By adhering to this plan of assessment, the investigation of the foetal heart action in labour has shown that both the rate and the amplitude of foetal heart deflections are relatively easily affected and clinical reliance on mere alterations in rate or regularity of the foetal heart sounds may lead to much unwarranted interference with the course of labour. Sinus arrhythmia is a common finding in foetal hearts and appears to have little clinical significance: it may possibly be explained on the basis of myogenic or neurogenic impulses from the "pacemaker". Pronounced slowing and irregularity of the foetal heart sounds and electrocardiographic recordings can be artificially produced by relatively little pressure by the hand upon the foetal skull through the maternal abdomen in both cephalic and breech presentations.

Any conclusions, therefore, regarding foetal distress as shown by alterations in the foetal heart action recordings, should be reached with much caution.

Twenty-one records were made of the foetal heart in prolonged labour (average duration over 63 hours). In 12 of these cases the amplitude of the R wave varied between 1-3 mm. and its width between 0·02-0·04 seconds. The findings are not of real significance in the estimation of foetal distress, but they tend to indicate a fall in amplitude, rate and duration of foetal deflections from the normal standard as compared with late pregnancy. No conclusions can be drawn from these few findings but it may be that a more perfect recording machine may throw new light upon this aspect of foetal physiology.

Discussion

While many earlier investigators have been intrigued by the possibilities of electrocardiographic and phonocardiographic technique in the study of the foetal heart, substantial advances in this subject have been limited by technical difficulties. The use of the modern preamplifier circuits (Smyth, 1953) and the cathode

ray tube (Gunn and Wood, 1953), have produced results far in advance of earlier methods and indicate that electrocardiography and heart sound recordings may provide further information concerning the foetal heart.

The standard of results in this series improved with experience and, although the earliest definite tracing was at the 17th week of pregnancy, further development may be anticipated in early recording. The work of Hoff *et al.* (1939) showed what could be achieved in experimental electrocardiography with the chick embryo, producing well developed complexes from the 24 somite stage (48 hours) by direct application of microelectrodes. The absolute minimum stage at which electrocardiographic recordings can be made has yet to be reached, but theoretically this should be as early as the 16-30 somite stage when, according to Arey's data (1940), fusion of the heart tubes takes place in the human embryo. Heard, Burkley and Schaefer (1936) recorded electrical impulses directly from the human foetus, removed by hysterotomy, as early as the 5th week of life and similar results were obtained by Marcel and Exchaquet (1938), showing the extent of early electrical potential changes arising from the foetal heart.

The value of combined potential and sound records is not primarily confined, however, to the early diagnosis of pregnancy: it extends to the diagnosis of intra-uterine life and death, and here the experience of many experimenters has been encouraging, for the recording of the foetal heart by electrocardiography or phonocardiography, either separately or simultaneously, has given uniformly accurate results.

Much work has yet to be done in the assessment of foetal distress by recording apparatus. It can be shown that marked variation of the foetal heart action can occur without apparent explanation, but it is reasonable to suppose that a more precise understanding of these variations can be obtained by graphic recordings.

The relationship of foetal size and maturity to recordings of the foetal heart promises to throw light on a new method of estimation of the duration of intra-uterine life.

The effects of anaesthesia, anoxia, drugs and maternal pyrexia, upon the foetus may become susceptible of fuller investigation.

Summary

1. Preliminary work shows that simultaneous foetal electrocardiography and phonocardiography is practical by a simple technique.

2. In a normal series of 110 unselected cases, at term, 98 per cent positive tracings were obtained.

3. Eighty-five per cent positive tracings were obtained in both groups (selected and unselected) from the 190 recordings from the 17th week of pregnancy to term.

4. The clinical possibilities of the technique in relation to obstetric problems are discussed.

I am indebted to Mr. M. W. B. Bulman and Mr. A. P. Bentall for access to their patients for the purpose of this study and for their interest and encouragement. I should like to acknowledge the help of General Radiological Ltd. (London) for the construction of the preamplifier and the use of modified apparatus. I have to thank Bowen & Co. Inc. (Maryland, U.S.A.) for supplying me with their special electrodes.

I wish to thank the East Anglian Regional Hospital Board for a research grant towards this study.

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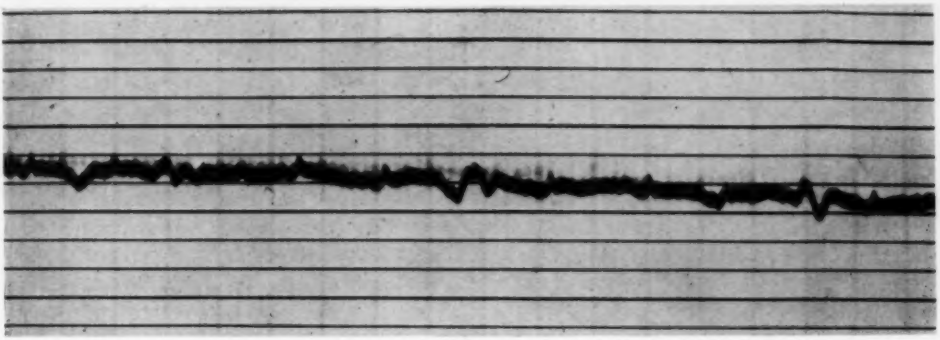

FIG. 1

Foetal electrocardiogram recorded at the 17th week of pregnancy.

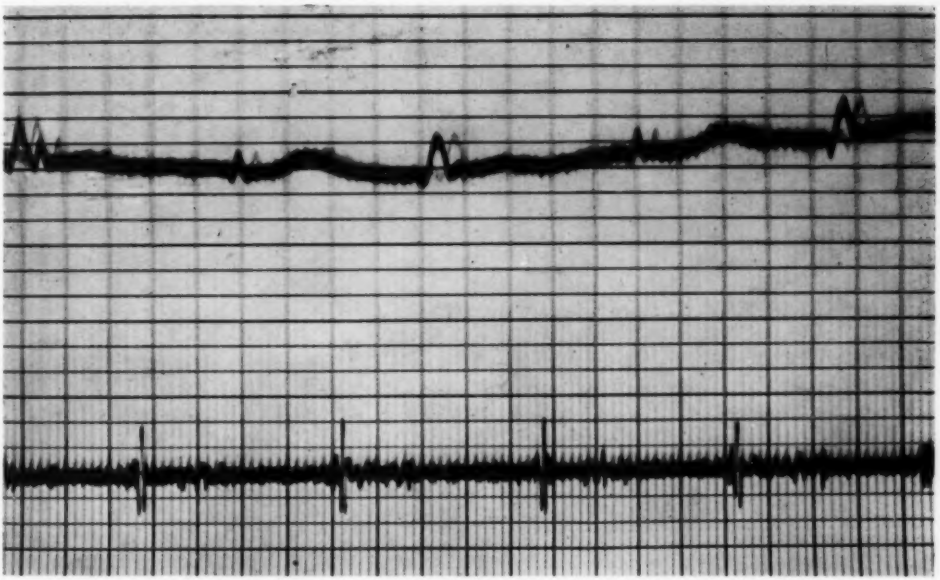

FIG. 2

Foetal electrocardiogram and phonocardiogram showing upward deflections of foetal and maternal hearts in a case of breech presentation.

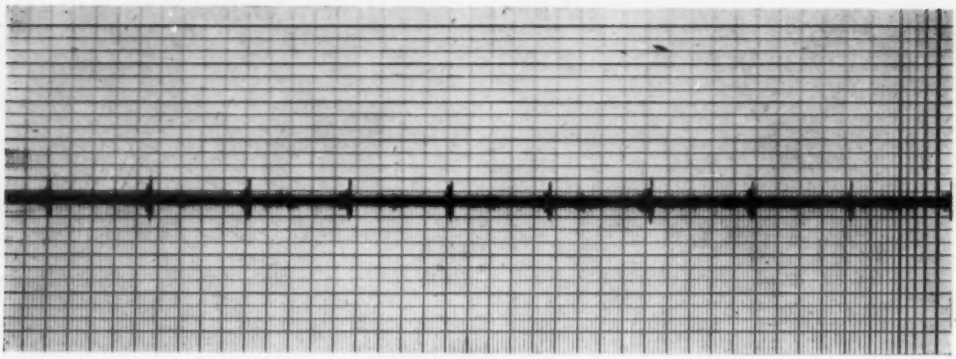

FIG. 3
Foetal phonocardiograph after 6 hours labour.

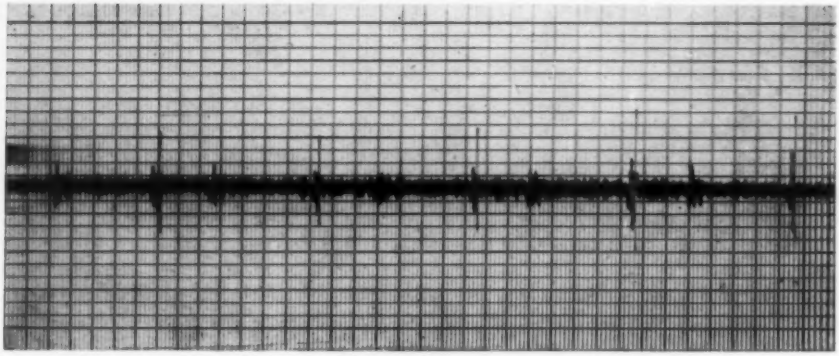

FIG. 4
Same case after 36 hours labour.

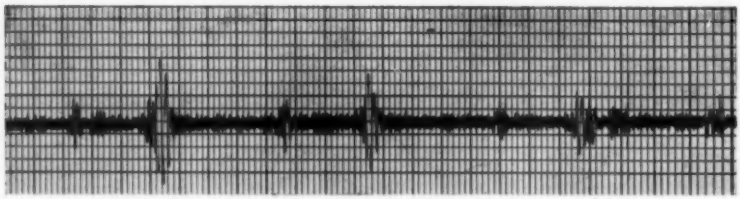

FIG. 5
Same case after 62 hours labour suggestive of foetal cardiac distress.

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POST-MENOPAUSAL BLEEDING ASSOCIATED WITH ENDOMETRIAL HYPERPLASIA

BY

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IN order to assess the importance of endometrial hyperplasia in relation to post-menopausal bleeding, a study was made of 1,000 cases of post-menopausal bleeding occurring in the Royal Samaritan Hospital for Women, Glasgow. These patients were admitted during the period between 1st January, 1941 and 27th June, 1947 and represent 4·31 per cent of the total of 23,200 gynaecological patients admitted to the hospital during that time. Only cases aged over 40 years and with a history of amenorrhoea for at least 1 year before the onset of bleeding were included in the series. Every patient answering these criteria was included, irrespective of the amount of haemorrhage, and cases with slight, blood-stained vaginal discharge were not omitted, even though this symptom was not the primary complaint.

CAUSAL LESIONS

From a study of the available records, the following conditions were found to be present:

Carcinoma of cervix	148
Prolapse (97 with obvious ulceration)	116
Active endometrial hyperplasia	95
Senile vaginitis	92
Cervical polyp	90
Carcinoma of body of uterus	89
Chronic cervicitis	76
Urethral caruncle	37
Inactive endometrial hyperplasia	31
Pessary ulceration of vagina	21
Fibroid polyp of uterine body	17
Fibro-adenomatous polyp of uterine body	15
Sarcoma of uterus	13
Pseudomucinous cystadenoma of ovary	13
Pyometra	13
Malignant ovarian tumours excluding granulosa cell tumours	13
Senile endometritis	7
Unspecified polyp of endometrium (tissue not available for histological examination)	5
Granulosa cell tumour of ovary	5
Papilliferous cyst of ovary	3
Fibroma of ovary	3
Primary carcinoma of vagina	3
Mixed mesodermal tumour of uterus	3
Carcinoma of vulva	2
Melanotic sarcoma of vulva	1
Carcinoma of Fallopian tube	1
Fibro-adenoma of ovary	1
Tuberculosis of endometrium	1

It should be noted that, in 106 cases in the series, no lesion capable of explaining the bleeding could be found. It also seems worthy of mention that, in some instances, more than one lesion was found to be present. Although the lesions listed may have been responsible for the post-menopausal bleeding, it is not suggested that they provide an explanation for the bleeding in every case in which they occurred.

INCIDENCE OF MALIGNANCY

It will be seen from the figures quoted above that malignant disease of the generative tract was found in 278 cases, constituting 27·8 per cent of the total of 1,000. Great variations of opinion are found in the literature on the question of the incidence of malignancy in post-menopausal bleeding, although to some extent these differences may be due to differing standards of what constitutes post-menopausal bleeding and to the small size of many of the series. Keene (1935) states that nearly two-thirds of these cases are malignant, Pemberton and Lockwood (1935) place the incidence of malignancy at about 50 per cent, while Kanter and

Klawans (1950) quote the high figure of 75 per cent. In the following list, the incidence of malignancy in series of cases of post-menopausal bleeding is given. The very high figure of 81·3 per cent of 395 cases cited by Geiger (1941) is probably due to the fact that his cases were drawn from a gynaecological tumour clinic.

Author	Total cases of post-menopausal bleeding	Percentage of malignancy
Herd (1930)	100	61
Kanter and Klawans (1932)	98	68·4
Burger (1933)	90	62·2
Fahmy (1933)	937	43·1
Geist and Matus (1933) ..	182	57·5
Schulze (1933)	315	68·2
Logwinsky (1935)	79	53·2
Wittenbourg and Zlatmann (1935)	100	41
Wittenbourg and Zlatmann (1935)—collected from literature	2,387	62·8
Wynne (1935)	71	19·7
Te Linde (1937)	349	53·3
Keene and Dunne (1938) ..	782	More than 60
Taylor and Millen (1938)	406	63
Geiger (1941)	395	81·3
Schwartz (1943)	114	43·1
Long (1945)	56	10·7
Cheek and Davis (1946) ..	514	36·1
Feeney (1947)	100	42
McFarlane (1947)	200	35
Husslein (1948a)	100	64
Lewin (1950)	583	73·1
Wagner (1950)	245	44
Jones and Cantor (1951) ..	244	54·9

It will be seen from the above list that the percentage of malignancy found in the present series is considerably lower than almost every comparable figure quoted in the literature. It is considered that there are two main reasons for this. The first of these is the scope of the present series. At the outset it was decided to include all patients with post-menopausal bleeding, irrespective of whether or not this was the primary complaint and irrespective of the actual blood loss. Thus cases of bleeding associated with ulcerated prolapse, in which the bleeding usually amounted to no more than slight blood-stained discharge, are second only to carcinoma of the cervix in the list of causal lesions. The second possible explanation is that the present series is much larger than most of those previously published and thus is more likely to present a true picture.

Endometrial Histology

The various benign histological pictures encountered in the endometrium will now be considered in turn.

Endometrial hyperplasia. The literature contains relatively few references to the incidence of endometrial hyperplasia in post-menopausal bleeding. In the following list, figures are given on this point, though the authors do not differentiate between active and inactive or "retrogressive" hyperplasia:

Author	Total cases of post-menopausal bleeding	Percentage with hyperplasia
Keene and Dunne (1938) ..	782	1·7
Geiger (1941)	395	1·2
Schwartz (1943)	114	7·0
Wagner (1950)	245	10·0
Jones and Cantor (1951) ..	244	3·6

It is apparent from the considerable variations noted above, that different authors vary widely in their interpretation of the term "endometrial hyperplasia". In the present series, hyperplasia of the endometrium was found 126 times (12·6 per cent). Although dilatation and curettage with histological examination of the tissue obtained were carried out in most cases, in a number of instances this procedure was omitted, particularly in patients with clinically obvious carcinoma of the cervix. It is thus possible that the true incidence of endometrial hyperplasia is higher than the figure obtained.

Active hyperplasia. Active hyperplasia of the endometrium was found 95 times (9·5 per cent). This condition is characterized by cystic dilatation of the glands, which show considerable disparity in size. The glands are lined by cuboidal or columnar epithelium and the cells of both glands and stroma show activity as evidenced by the presence of mitotic figures. The general

pattern is essentially similar to that seen in "metropathia haemorrhagica" occurring during the reproductive period of life, except that the areas of stromal haemorrhage and necrosis frequently seen in that condition are absent. In a small proportion of cases cystic dilatation of the glands is not a prominent feature, and the glands tend to be closely packed together, with little intervening stroma. The histological features of active hyperplasia are seen in Fig. 1.

The 95 cases of post-menopausal bleeding associated with active hyperplasia occurred from 1 to 35 years after the menopause and the distribution is shown in Table I.

TABLE I

Years after Menopause in Cases of Active Hyperplasia

Years after Menopause	Number of Cases	Per cent
5 and under	40	42·1
6—10	23	24·2
11—15	13	13·7
16—20	10	10·5
Over 20	9	9·5

Type of menopause. In 91 of the 95 cases with active hyperplasia the menopause occurred naturally. In 3 instances the hyperplasia developed after a menopausal dose of deep X-ray therapy for abnormal uterine bleeding, and in the remaining case the menopause followed bilateral oöphorectomy. The last patient was treated in another hospital and clinical details could not be obtained.

Inactive hyperplasia. Inactive hyperplasia of the endometrium was found 31 times (3·1 per cent). In many of these cases the appearances were confined to a single polypoid portion of endometrium and in the remainder the condition was more generalized. Inactive hyperplasia was considered to be present when the glands showed marked cystic dilatation, the degree of enlargement frequently being much greater than that seen in the active type. The epithelium lining the glands is flattened, with cells of inactive type and the stroma has a loose and cellular arrangement. The histological features of inactive hyperplasia are seen in Fig. 2.

Although the term "inactive hyperplasia" has been used in describing the present specimens, there appears to be some doubt as to whether the use of the word "hyperplasia" is appropriate. There would seem to be grounds for using an alternative term such as "inactive polyp" or "senile polyp" in describing such specimens. Among the reasons for this view are the entirely inactive appearance, and the fact that many of them consist of a single polypus. In addition, the appearances differ completely from those of active hyperplasia and in no case in the present investigation were the changes of "active hyperplasia" and "inactive hyperplasia" found in the same specimen.

A number of writers have described endometrial appearances similar to those just discussed. Novak and Richardson (1941) give a detailed description of the post-menopausal endometrium in general as opposed to the picture found in post-menopausal bleeding. They noted that typical hyperplasia can be found long after the menopause, although the pattern was frequently "retrogressive" rather than active. They considered that the source of oestrogen was extra-ovarian, probably the adrenal cortex.

Similar findings are reported by Kottmeier (1947), Gianaroli (1947) and Speert (1949), the specimens described in the last-named paper being from cases of prolapse occurring beyond the menopause and unassociated with uterine bleeding. Lund and Dougherty (1950) do not consider that inactive hyperplasia signifies coexisting oestrogenic stimulation. They state that patients probably do not bleed from this condition and that its discovery is incidental. The 31 cases of post-menopausal bleeding associated with inactive hyperplasia of the endometrium occurred from 3 to 27 years after the menopause, and the distribution is shown in Table II.

TABLE II

Years after Menopause in Cases of Inactive Hyperplasia

Years after Menopause	Number of Cases	Per cent
5 and under	3	9·7
6—10	9	29·1
11—15	8	25·7
16—20	5	16·1
Over 20	6	19·4

It will be seen, when the figures in Tables I and II are compared, that active hyperplasia associated with post-menopausal bleeding is particularly prone to occur shortly after the menopause, whereas inactive hyperplasia is more evenly distributed throughout the age groups examined. In 30 of these cases the menopause occurred naturally and, in the remaining instance, an artificial menopause had been induced with radium because of abnormal uterine bleeding.

Other non-malignant endometrial appearances. The following additional non-malignant endometrial pictures were found:

Endometrial atrophy	51 cases
Fibro-adenomatous polyp ..	15 cases
Senile endometritis	7 cases
Secretory endometrium ..	4 cases
Tuberculosis	1 case

Brief reference will now be made to each of these groups in turn.

Endometrial atrophy. Here the endometrium was thin and scanty, with infrequent, inactive glands and a fibrous stroma. The surface epithelium usually consisted of a single layer of cuboidal cells. The histological appearances of endometrial atrophy are seen in Fig. 3. The 51 cases of endometrial atrophy associated with post-menopausal bleeding occurred from 1 to 34 years after the menopause, the details being shown in Table III.

TABLE III

Years after Menopause in Cases of Endometrial Atrophy

Years after Menopause	Number of Cases	Per cent
5 and under	17	33·3
6—10	11	21·5
11—15	11	21·5
16—20	9	17·7
Over 20	3	5·9

Fibro-adenomatous polyp. Specimens classified under the heading of fibro-adenomatous polyp consisted of single portions of tissue, in which inactive glands of endometrial type were set in a dense, fibro-muscular tissue, quite unlike endometrial stroma. The histological picture is shown in Fig. 4. The bleeding associated with fibro-adenomatous polypus occurred from 3 to 25 years after the menopause.

Senile endometritis. In this condition the endometrium was scanty and the stroma was densely infiltrated with lymphocytes and plasma cells in considerable numbers. The discovery of senile endometritis associated with post-menopausal bleeding was made from 6 to 34 years after the menopause. Pyometra was present in 5 of these patients and senile vaginitis in 1 further instance.

Secretory endometrium. The appearances in these specimens were essentially similar to those seen during the reproductive period of life and do not necessitate detailed description. In this group the time after the menopause was 1 year in 1 case, 2 years in 2 cases and 6 years in the remaining instance. All 4 patients were parous and were aged 47, 43, 42 and 52 years respectively. One patient, aged 42, had had a menopausal dose of deep X-ray therapy for abnormal uterine bleeding 2 years previously. This finding of occasional examples of secretory endometrium associated with post-menopausal bleeding is interesting, and has received practically no attention in the literature.

Tuberculosis. The specimen from this case consisted of tuberculous granulation tissue. This patient was aged 46 years and had had a natural menopause 19 years previously. Although tuberculosis of the endometrium is now known to be a fairly common condition, it is rarely encountered after the menopause.

RELATIONSHIP BETWEEN ENDOMETRIAL HYPERPLASIA AND CARCINOMA OF THE UTERINE BODY

The relationship between endometrial hyperplasia and carcinoma of the uterus has been discussed by a number of authors. Taylor (1932) analyzed 152 cases of uterine carcinoma and found that associated hyperplasia was present in 15. He stresses the difficulty of diagnosis of endometrial hyperplasia in such cases. Novak and Yui (1936) studied 104 cases of uterine cancer. They found associated endometrial hyperplasia in 25 out of 64 of these, and the remaining 40 were excluded because sections through non-cancerous mucosa were not available for study. This matter is also discussed by Taylor and Millen (1938), Novak (1944a), Mussey, Dockerty and Masson (1947) and

Corscaden (1951). Atypical endometrial hyperplasia simulating carcinoma is described in detail by Novak and Rutledge (1948).

In the present series there were 89 cases of carcinoma of the uterine body, of which 76 were adenocarcinoma, including 3 examples of adenoacanthoma, 10 were solid carcinoma and 3 were squamous cell carcinoma. In many instances only malignant tissue was present in the material available for study. In the remainder, active hyperplasia was found 7 times, inactive hyperplasia 8 times, endometrial atrophy 5 times and fibro-adenomatous polyp once. The histological appearances of associated uterine carcinoma and endometrial hyperplasia are seen in Figs. 5 and 6.

In 2 cases of adenocarcinoma of the uterine body, simple active hyperplasia of the endometrium had been noted at diagnostic curettage on a previous occasion. The first patient was aged 62 years when hyperplasia was discovered and 69 when adenocarcinoma was found to have developed. The second patient had hyperplasia for which she was given a "menopausal dose of deep X-ray therapy at 58 years" and adenocarcinoma was discovered 6 years later. While the occurrence of these 2 cases shows beyond doubt that active hyperplasia may be followed by adenocarcinoma at a later date, the present series of cases does not suggest in any way that this is a common occurrence.

Relationship between Post-Menopausal Bleeding and Granulosa Cell Tumour of the Ovary

Many writers have discussed the relationship between post-menopausal bleeding and granulosa cell tumour of the ovary: Novak and Brawner (1934), Bland and Goldstein (1935), Meigs (1935), Novak and Gray (1936), Schiller (1936), Pratt (1937), Chaney and Greenblatt (1938), Varangot (1938), Bergstrand (1939), Dockerty and MacCarty (1939), Dockerty and Counseller (1940), Karsner (1940), Traut and Marchetti (1940), Novak (1941), von Pallos and Treite (1941), Henderson (1942), Novak (1942), Novak (1944b), Hodgson, Dockerty and Mussey (1945), Louw (1946), Rhoads (1946), Dockerty (1947), Kottmeier (1947), Mussey, Dockerty and Masson (1947), Husslein (1948b), Novak (1948), Falls, Ragins and Goldenberg (1949), Lund and Dougherty (1950), Haines and Jackson (1950), Corscaden (1951), Diddle (1952).

Five cases of granulosa cell tumour were encountered in the present series. In 1 of these the tumour only was removed and no endometrium was available for study. In the other 4, active endometrial hyperplasia was found to be present.

Association with oestrogen therapy. A number of writers have discussed the relationship between post-menopausal bleeding and oestrogen therapy and have condemned the indiscriminate use of oestrogens in post-menopausal patients. The whole matter is reviewed in detail by Novak (1944a), and the following authors also draw attention to this question: Cheek and Davis (1946), Noyes (1945), Feeney (1947), Kottmeier (1947), Kanter and Klawans (1950), Lund and Dougherty (1950).

A history of previous administration of stilboestrol or other oestrogen was recorded in only 12 cases in the whole of the present series of 1,000, but it is likely that the true figure was higher than this. In 4 of these 12 cases active endometrial hyperplasia was found to be present.

Summary

A study has been made of 1,000 cases of post-menopausal bleeding, only patients aged over 40 years and with a history of amenorrhoea for at least 1 year before the onset of the bleeding being included. These patients represent 4·31 per cent of the 23,200 gynaecological patients admitted during the period under review.

Malignant disease of the generative tract was found in 278 cases (27·8 per cent). Endometrial hyperplasia occurred in 126 instances (12·6 per cent), 95 of these specimens showing active hyperplasia and the remainder inactive hyperplasia.

Endometrial atrophy was found in 51 cases, fibro-adenomatous polyp in 15 cases, senile endometritis in 7 cases, secretory endometrium in 4 cases and endometrial tuberculosis in 1 case.

In 89 patients carcinoma of the uterine body was present. In a number of these, non-malignant tissue was also found, inactive hyperplasia

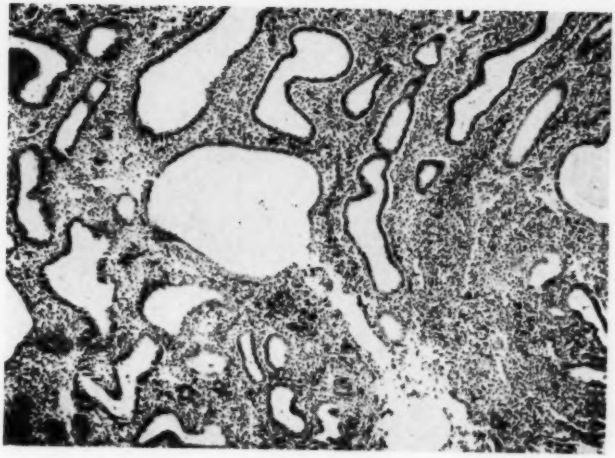

FIG. 1
Active hyperplasia of the endometrium. ×45.

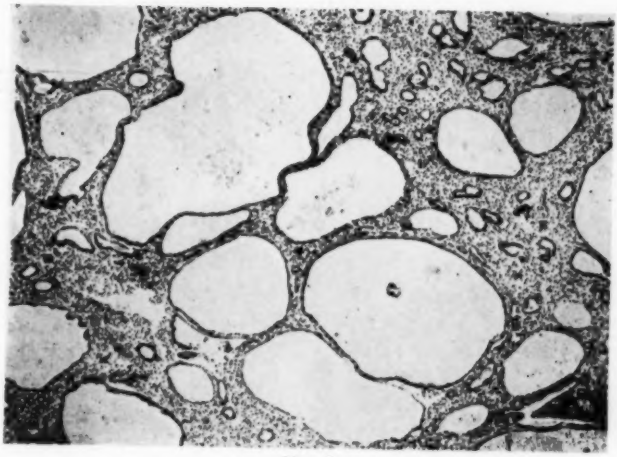

FIG. 2
Inactive hyperplasia of the endometrium. ×45.

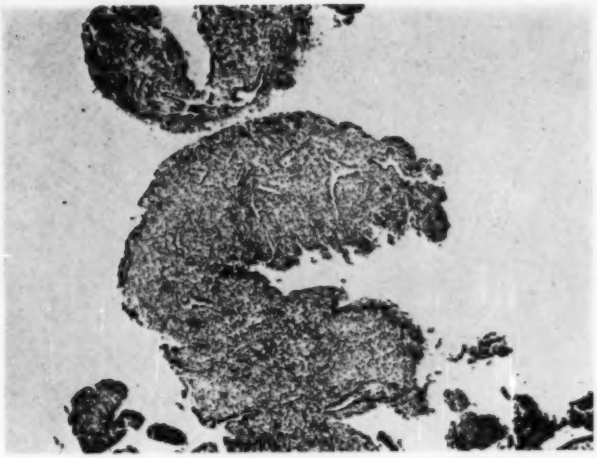

FIG. 3
Endometrial atrophy. ×45.

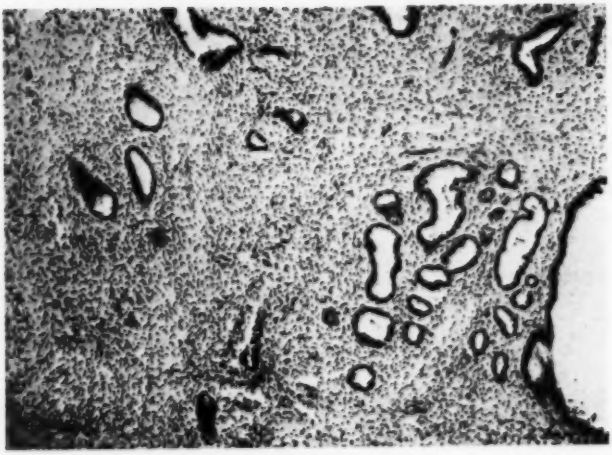

FIG. 4
Fibro-adenomatous polyp. ×45.

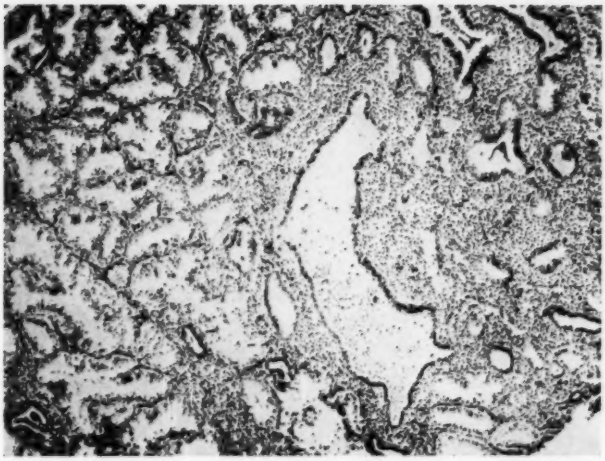

FIG. 5

Adenocarcinoma of uterus associated with active endometrial hyperplasia. ×45.

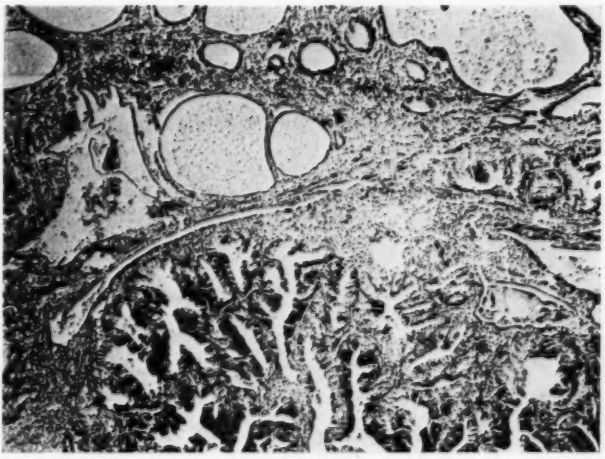

FIG. 6

Adenocarcinoma of uterus associated with inactive endometrial hyperplasia. ×45.

occurring 8 times, active hyperplasia 7 times, endometrial atrophy 5 times and fibro-adenomatous polyp once. In 2 cases with adenocarcinoma, a previous curettage had shown simple active hyperplasia.

Five cases were associated with granulosa cell tumour of the ovary and a history of recent administration of oestrogen was obtained in 12 instances.

Acknowledgments

We should like to express our thanks to Doctors McIntyre, Hewitt and Clement for permission to study case records from their files.

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N-ALLYLNORMORPHINE (LETHIDRONE) IN THE TREATMENT OF NEONATAL ASPHYXIA

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N-ALLYLNORMORPHINE first prepared in 1941 by McCawley, Hart and Marsh (1941) was found to antagonize respiratory depression due to morphine in experimental animals (Unna, 1943). Fraser *et al.* (1952) found that in methadone (amidone) poisoning it induced spectacular and possibly lifesaving effects in the human subject. Eckenhoff *et al.* (1952) and Adriani and Kerr (1953) showed it to be equally effective against similar effects produced by Demerol (pethidine). It is quite ineffective in respiratory depression produced by the barbiturates, the inhalation anaesthetics and any drug not pharmacologically related to morphine. It is believed to act by replacing the methyl group of the narcotic drug in the receptor organ by its own allyl group. In consequence, the respiratory depressant effects are overcome, but the sedative and analgesic effects remain unaltered. N-allylnormorphine produces analgesia and sedation, and in large doses can, itself, cause respiratory depression. Clinically, it has been used in patients suffering from overdosage of morphine, pethidine or amidone, or showing special idiosyncrasy to these drugs. It has proved effective in such cases in the relief of respiratory depression in doses of 10 to 40 mg., but Fraser *et al.* (1952) warn that it is not entirely devoid of toxic properties and that it would probably be dangerous to exceed 40 mg. in a single dose. They regard N-allylnormorphine as the ideal analeptic for the treatment of acute and narcotic poisoning since it is effective in small doses and its effects are well maintained. In one of the recorded cases 375 mg. of nikethamide showed no effect after 20 minutes, whereas an intravenous dose of 40 mg. of N-allylnormorphine produced spectacular reversal of induced respiratory depression within 3-4 minutes.

In obstetrics, its use has so far been limited, but two methods of its employment have been suggested. Firstly, where opiates and other analgesics have been used during labour, the intravenous injection of 10 mg. of N-allylnormorphine about 10 minutes before delivery is expected has been used in the prevention of neonatal asphyxia. Eckenhoff *et al.* (1953) have found, in a large series of mothers treated routinely in this way, that the number of infants needing resuscitation was much smaller than in a control series. Alternatively, the drug may be given, either intravenously into the umbilical cord or intramuscularly into the buttock, to the newborn infant where it has proved difficult to establish respiration on account of the effects of morphine, pethidine or similar drugs administered to the mother during labour.

The present paper constitutes a report on our early experience of the use of N-allylnormorphine by the latter method. It is very difficult to assess the effect of a drug administered to the mother by the former method described above, since the response of the infant to sedatives used in labour varies so much in individual cases. We have restricted its use, therefore, to infants who have not shown signs of respiration within a short time of delivery in cases in which the mother has been given

morphine or pethidine during labour. A standard dosage of 0·25 mg. has been used in each case and this has been obtained from ampoules of "Lethidrone" containing 1 mg. in 2 c.cm. (that is 1/20th of the present standard dilution of "Lethidrone" as used for adults). Adriani and Kerr (1953) used a dosage of 2·5 mg. in 4 cases and claimed an effect within 30 seconds in each case. Eckenhoff *et al.* (1953) in 12 cases used doses of 0·1 or 0·2 mg. and claimed dramatic and excellent results in 11 out of 12 cases.

A third possible method of administration is the use of N-allylnormorphine whenever morphine is given in order to prevent the development of respiratory depression. That this method may be successful is suggested by the finding of Adriani and Kerr that premedication of rats and dogs with N-allylnormorphine increases the resistance to morphine so that lethal doses were tolerated without the usual respiratory and circulatory depression. This, however, remains a method which requires further investigation in the experimental animal.

In cases where very large doses of narcotics have been used during labour, the administration of N-allylnormorphine into the cord, immediately after birth and before interruption of the placental circulation, may prove a valuable prophylactic.

The present series consists of 8 cases which have been treated at this hospital during the past 5 months. These are as follows:

Case 1. Mrs. J. O'N., a primigravida, aged 21, was delivered spontaneously after a labour lasting 13 hours 5 minutes. Four and three-quarter hours before delivery, morphine gr. ¼ was injected. The child, weighing 7 pounds 8 ounces, showed complete apnoea at birth and 15 minutes after delivery had not breathed. Lethidrone 0·25 mg. was injected intramuscularly into the buttock and 2 minutes later respiration began and was rapidly established. Subsequent progress of the child was excellent.

Case 2. Mrs. E. T., aged 27, para-2, had a brisk haemorrhage at the onset of labour at the 33rd week. There was no evidence of placenta praevia nor of pregnancy toxaemia, but morphine gr. ¼ was given hypodermically on admission to hospital. One and a quarter hours later she was delivered of a live child weighing 5 pounds 4 ounces, which showed asphyxia livida at birth. 0·5 mg. of Lethidrone was injected into the umbilical vein and respiration was rapidly established within 30 seconds. The child gave no further anxiety.

Case 3. Mrs. I. C., primigravida, aged 23 years, had a normal delivery of a child weighing 6 pounds 8¼ ounces after a labour lasting 7 hours 45 minutes. There was a minor degree of cephalo-pelvic disproportion, and the patient was particularly apprehensive. In the management of this labour, pethidine mg. 150 had been given 5¼ hours before delivery and 100 mg. 2¼ hours before delivery. The child was born in a state of asphyxia pallida and had not breathed 10 minutes after delivery. Following the injection of 0·25 mg. of Lethidrone intramuscularly, respiration was well established within 2 minutes and thereafter satisfactorily maintained.

Case 4. Mrs. M. R., aged 20, primigravida, showed a toxaemia of extreme severity at the 37th week of her pregnancy. Her blood pressure was then 205/135, the urine contained 12 mg. per cent of albumen and there was gross oedema. In view of the extreme severity of her toxaemia, morphine gr. ¼ was given as a sedative, and 6 hours later Caesarean section undertaken. The child, which weighed 4 pounds 5 ounces was in a state of asphyxia pallida and 12 minutes after delivery had made no respiratory effort whatever. 0·25 mg. Lethidrone was given into the umbilical vein and respiration was established 1 minute later and subsequently well maintained.

Case 5. Mrs. R. H., aged 20, gravida-3, gave a history of 2 early abortions. Labour began following a medical and surgical induction at the 41st week of pregnancy. The child was large (10 pounds) and the labour difficult so that pethidine 150 mg. 9 hours before delivery was followed by 100 mg. 3 hours before a mid-forceps delivery. Fifteen minutes later respiration had not been established, and Lethidrone 0·25 mg. intramuscularly was followed within 30 seconds by obvious respiratory excursion of the chest and strong crying in two minutes. The child's further progress was uneventful.

Case 6. Mrs. B. H., aged 23, primigravida, had a surgical induction of labour at the 37th week on account of severe toxaemia with massive oedema, headaches and blood pressure raised to 160/120. She was heavily sedated with pethidine during labour, 100 mg. being given 13 hours, 150 mg. 4 hours and 100 mg. 55 minutes before delivery. The child made no respiratory effort following delivery, but after 3 minutes Lethidrone 0·25 mg. was given into the umbilical vein. Within 30 seconds respiration had begun, then 90 seconds after injection the child was crying strongly. Subsequent progress of both mother and child was satisfactory.

Case 7. Mrs. A. W., aged 25, primigravida, underwent trial labour at the 41st week of her pregnancy on account of cephalo-pelvic disproportion due mainly to the large size of the child—10 pounds 13 ounces. After 25 hours it became obvious that vaginal delivery was impracticable and so Caesarean section was carried out. Morphine gr. ¼ was given 8 hours, and repeated 4 hours 20 minutes before operation, and 7 minutes after delivery the infant had shown no sign of respiration. Lethidrone 0·5 mg. was given into the umbilical cord and satisfactory respiration began within 30 seconds, and was well established 3 minutes after injection.

Case 8. Mrs. G. L., aged 28, gravida-3, gave a history of two 8-week abortions. Labour was induced surgically at the 41st week of pregnancy. Sedation included pethidine mg. 150 and mg. 100 given 22 and 9 hours respectively before delivery, labour having lasted 26 hours. A tentative attempt at forceps delivery was made but was abandoned on account of the incomplete dilatation of the cervix and the extremely high head. Delivery was effected by lower segment Caesarean section. Anaesthesia with gas, oxygen, Flaxedil and cyclopropane had been maintained for 45 minutes before delivery of the child and this was doubtless responsible for complete failure of resuscitation. In view of the fact that pethidine had been given in large doses during labour, Lethidrone 0·5 mg. was given intramuscularly 20 minutes after delivery, but proved ineffective. At post mortem there was no intracranial injury, but complete atelectasis of both lungs due no doubt to the respiratory depression caused by the inhalation anaesthetics.

Discussion

The above series is too small to do more than suggest that in N-allylnormorphine we have a drug which may be of great value in obstetrics, and which may have many useful clinical applications. When this investigation was first begun it was felt that the drug would be required only in cases where an error of judgment had led to over-dosage with sedatives or to the administration of sedatives so late in labour that delivery followed after a very short interval. Further experience, however, has already shown us that the drug has a much wider range of usefulness. In the first place, respiratory depression may occur in the infant where delivery is achieved earlier than was expected after the administration of a large dose of sedative, either as a result of a rapid spontaneous advance, or because failure of the foetal heart, prolapsed cord, or other evidence of foetal distress has demanded instrumental delivery. In severe toxaemia or eclampsia, where heavy sedation of the mother is required for the control of convulsions, the child may be delivered either by Caesarean section or per vaginam at a time when, like the mother, he is heavily under the influence of such sedatives, and here, too, N-allylnormorphine may have a useful part to play. In trial labour and in other prolonged and arduous labours, we have been encouraged already to use sedatives more freely and sometimes in larger dosage than we should have been prepared to use before we had had some experience of this drug. In the very nervous patient or in the patient admitted without previous sedation late in labour, morphine or pethidine can be given with less fear of inducing a dangerous neonatal asphyxia should delivery follow very quickly. In Caesarean section full anaesthetic premedication may be used if there is any special indication for it, and this may have its advantages in certain cases of pulmonary or cardiac disease, so that the amount of inhalation anaesthetics may be kept to a minimum.

In all these types of case it is to be noted that N-allylnormorphine is ineffective against respiratory depression due to barbiturates and that the sedation used should be restricted to morphine, pethidine, amidone and other pharmacologically similar drugs.

In conclusion, we believe that N-allylnormorphine is a drug which has much to offer to the obstetrician, and there are many types of case in which a greater freedom in the use of sedatives is an advantage which is available only when we know that respiratory depression in the foetus can satisfactorily be antagonized should this prove necessary. In this connection it is noteworthy that in several of our cases the drug was dramatically effective where the dosage of the sedative was not excessive by ordinary standards, and in some, the interval between the last dose of the drug and delivery was considerable. It would seem, therefore, that there is a place for this drug, not only where there has been high dosage or an abnormally short drug-delivery interval, but in a number of cases in which the infant shows special susceptibility to the drug. N-allylnormorphine should therefore be used in all cases in which respiration is not established shortly after delivery where, during the mother's labour, any of the appropriate sedatives has been used.

Summary

Eight cases of neonatal asphyxia have been treated with N-allylnormorphine. In 7 of these, where the asphyxia appeared to be due to the effects of morphine or pethidine, dramatic results were obtained. In the 8th where inhalation anaesthesia was probably responsible, no response was elicited.

We are indebted to Messrs Burroughs Wellcome & Company for supplies of a special packing of Lethidrone and for guidance as to dosage.

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PREVENTION OF VAGINITIS AFTER MAJOR GYNAECOLOGICAL OPERATIONS WITH MEDICATED ETHYL-CELLULOSE JELLIES

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POST-OPERATIVE infection is a common sequel of operations on the vagina. While in many cases these infections are slight and limited to the actual field of the operation, severe and spreading infections do sometimes occur, proceeding even to abscess formation or septicaemia. The present communication concerns a study of the changes in the vaginal flora after gynaecological operations, and particularly vaginal operations with reference to post-operative infections such as vaginitis and cystitis.

It also reports on an attempt to prevent and treat post-operative infections by a method of intra-vaginal therapy using medicated jellies. In a previous study (Brand, 1953) carried out at the Elizabeth Garrett Anderson Hospital, this method of intra-vaginal therapy was found to be effective in the treatment of vaginal infections. The treatment was also found to be convenient and simple in use.

CLINICAL MATERIAL AND PROCEDURE

The clinical material on which this study is based consisted of 93 patients who underwent various gynaecological operations. In all of these a high vaginal swab was taken on admission and examined by direct film, saline preparation and culture, both aerobic and anaerobic.

Pre-operative Treatment

This consisted in all cases of twice daily douching with a mild antiseptic in the cases with a clean healthy vagina and a grade 1 flora. Where signs of infection were present penicillin pessaries each containing 60,000 units were inserted night and morning. If an ulcer of the cervix was found in complete procidentia, packs impregnated with ichthammol and glycerine or flavine and paraffin were inserted night and morning. Latterly infected cases have been treated with sulphathiazole jelly. All patients in both groups had 6 vitamin tablets and 3 ferrous sulphate tablets daily throughout their stay in hospital.

In all cases the vaginal flora was normal at the time of operation and a catheter specimen of urine was sterile on culture.

At the conclusion of the operation in cases of prolapse repair a pack was inserted into the vagina and removed 24 to 48 hours later. In treated cases, treatment was commenced after removal of the pack.

CONTROL SERIES

Post-operative Treatment in the Control Series

This group consisted of 43 cases. On removal of the pack the routine treatment employed in the hospital before the institution of this study was carried out. This consists in twice-daily cleansing of the vulva with sterile cotton wool containing a mild antiseptic. The external wound and the vaginal orifice were then dusted with bismuth subgallate powder (Dermatol). Intravaginal therapy was not given during the first week though, in cases where there was offensive or blood-stained discharge during the second week, low pressure irrigations were given. Patients showing symptoms or signs of post-operative

infection received systemic treatment with chemotherapy or antibiotics.

The following operations were performed in the 43 control cases:

"Manchester" (Fothergill) repair	14
Anterior and posterior colpo-perineorrhaphy	12
Posterior colpo-perineorrhaphy ..	5
Anterior colporrhaphy	1
Repair of urethrocele	3
Vulvectomy	1
Vaginal hysterectomy	1
Abdominal total hysterectomy ..	2
Dilatation and curettage	4
Total ..	43

Results in the Control Series

Vaginal swabs were examined at frequent intervals in the control cases and the results may be summarized as follows:

A change was noted in the reaction of the vagina. Before operation, the *p*H was found to be between 4 and 5·5. After operation the acid secretion of the vagina was modified by dilution of vaginal secretions with blood and the *p*H was found to lie between 6·5 and 8·5.

Saline preparations contained a greatly increased number of red blood cells and leucocytes. Direct films stained by Gram's method showed an increase in the number of bacteria with disappearance of Döderlein's bacillus. The number of organisms was relatively small in the first few days after operation but a very marked increase was noted on about the 6th or 7th post-operative day.

In the first few days after a major vaginal operation, cultures yielded a mixed flora, generally consisting of coliform bacilli, streptococci, staphylococci, and diphtheroids. Later, pathogenic or potentially pathogenic organisms established themselves and generally one particular type of organism predominated. Coliform bacilli (*Bacterium coli commune* in 19 cases, *Bacillus lactis aerogenes* in 1 case and paracolon bacillus in 1) often associated with *Streptococcus faecalis*, were the predominating organisms in 21 cases. In 9 cases, *Bacillus proteus* was the predominating organism; *Staphylococcus pyogenes* was found in 6 cases and streptococci in 4 cases. The streptococci were found to be of the Beta haemolytic type, Lancefield's Group A in 2 cases and *Streptococcus faecalis* in 2 cases. A normal flora was found in 3 cases following dilatation and curettage.

Post-operative Infections in Control Cases

Vaginitis occurred in 11 cases and cystitis in 13 cases. In 4 cases both complications occurred. The same organism was responsible in 3 cases. In the fourth the vaginitis was caused by *B. proteus* and the cystitis by *Staph. pyogenes*. In 6 cases the predominant pathogenic organism was *B. proteus*; *Staph. pyogenes* was found in 3 cases and Beta haemolytic streptococcus in one case. A trichomonas vaginitis developed on the 6th post-operative day in 1 case; this was thought to be a relapse of an infection which had existed before operation.

In 18 cases systemic treatment was given by chemotherapy or antibiotics, the choice of treatment depending on the sensitivity of the pathogenic organism present. All pathogens isolated in cases of vaginitis and cystitis were tested for sensitivity by the disc technique of Fairbrother and Martyn (1951), using sulphonamide, streptomycin, chloramphenicol and penicillin. One patient suffered from a staphylococcal vaginitis with a cellulitis of the posterior vaginal wall, and remained in hospital 5 weeks before healing was complete.

The heaviest growths of pathogenic organisms were yielded from cases following major vaginal operations such as "Manchester" repairs and anterior and posterior colpo-perineorrhaphy. After dilatation and curettage the vaginal flora returned to normal in 48 hours. After abdominal total hysterectomy the changes in the vaginal flora differed considerably from those seen after major vaginal operations; stained films showed vaginal squames in excess of leucocytes and on culture a scanty growth of organisms was obtained.

In the cases where vaginitis occurred the most severe infections on clinical grounds were those caused by *Staph. pyogenes* and *B. proteus*. These cases required intensive treatment with antibiotics.

Treated Series

Post-operative Treatment in Treated Series

The treated series consisted of 50 cases; medicated jellies were inserted into the vagina on alternate days (3 applications weekly) during the post-operative stay in hospital which lasted 2 weeks in most cases. The jelly was inserted by means of a disposable paper applicator which was used once only.

As previously reported (Brand, 1953), the ethyl cellulose jelly may be medicated with a variety of substances. For the purpose of the present investigation, three different jellies were used, namely proflavine jelly 0·2 per cent, sulphathiazole jelly 10 per cent, and lactic acid jelly 5 per cent. No other treatment was used in the treated group unless evidence of infection appeared, in which case systemic treatment with chemotherapy or antibiotics was instituted. The jelly was well retained and the findings confirmed previous reports by Willcox (1953) who demonstrated persistence of jelly after 72 hours and by Brand (1953). Proflavine was evident by its colour 3 to 4 days after insertion and sulphathiazole and lactic acid were similarly well retained.

The 50 cases in the treated group were divided up as follows: proflavine jelly 22 cases, sulphathiazole jelly 18 cases and lactic acid 10 cases. The following operations were performed:

Proflavine Jelly	
"Manchester" repair	8
Anterior and posterior colpoperineorrhaphy	6
Posterior colporrhaphy	3
Vulvectomy	1
Cervical biopsy	2
Vaginal hysterectomy	2
Sulphathiazole Jelly	
"Manchester" repair	6
Anterior and posterior colpoperineorrhaphy	6
Repair of urethrocele	2
Posterior colporrhaphy	2
Vaginal hysterectomy	2
Lactic Acid Jelly	
"Manchester" repair	4
Anterior and posterior colpoperineorrhaphy	3
Posterior colporrhaphy	1
Vaginal hysterectomy	2

Results in the Treated Series

Vaginal swabs were examined before and after operation in exactly the same way as in the control series. It was found that potentially pathogenic organisms appeared in the treated group as in the control group, the striking difference between the two groups being the low incidence of frank vaginitis, in spite of the presence of these potential pathogens. The organisms isolated may be tabulated as follows:

Organisms isolated from the Vagina in the Post-operative Period in the Treated Group

	No. of Cases
Bact. coli	29
B. proteus	3
Staphylococcus pyogenes	10
Streptococcus faecalis	7
Beta haemolytic streptococcus	1

It is unfortunate for the purpose of this study that at the time it was undertaken there was a minor outbreak of infection with *Staph. pyogenes*. This was traced to a carrier in the nursing staff in the operating theatre. The carrier was removed from duty in the theatre and the outbreak came to an end.

Post-operative Infections in Treated Cases

Frank vaginitis with inflammation and pus formation occurred in 3 cases in the treated group. All received proflavine jelly and in all 3 the predominating organism was a *Staph. pyogenes*, though in 1 case *B. proteus* was grown as well. It is possible, though difficult to prove, that these 3 cases were infected at the time of operation by the carrier in the theatre. Vaginitis due to *B. proteus*, encountered in 6 cases in the control series, was not seen in the treated series.

Cystitis occurred in 15 cases in the treated group; it occurred in 7 cases in the proflavine group, and was associated with vaginitis in 2 of these. Cystitis also occurred in 5 cases in the sulphathiazole group and in 3 cases in the lactic acid group.

Other post-operative infections in the treated group were 1 case of post-operative chest infection and 1 septic finger.

Seventeen patients in this group required

treatment with antibiotics or chemotherapy, 15 on account of urinary tract infection.

Discussion

This study afforded an opportunity of testing the effects of a comparatively new form of vaginal therapy after gynaecological operations and also of studying in a control series of cases the bacteriological changes which occur in the vagina. The first effect of a major vaginal operation is neutralization of the normally acid vaginal secretion by blood. This is followed by invasion by mixed organisms. On the sixth or seventh post-operative day, a further invasion appears to occur and often at this stage pathogenic organisms are found in more or less pure culture. It is at this stage that clinical vaginitis is likely to become apparent and it also seems likely that, if a means can be found of preventing this, the post-operative course will be smoother and the incidence of local septic complications, or even of extension of infection beyond the vagina, may be considerably lowered.

It appears that this object may be achieved by local vaginal therapy. The method employed in this series consisted of the application of medicated ethyl cellulose jellies using disposable paper applicators. Three main advantages were noted with this method:

1. The method is simple in use and proved acceptable to the patients. The applicator is small and the treatment can be given without undue discomfort.

2. The applicator is used once only and then discarded. This disposed of the risk of cross infection.

3. The ethyl cellulose jelly is well retained and the medicament remains in the vagina for at least 3 days. Treatment is therefore adequate when given only on alternate days or 3 times a week.

The incidence of vaginitis was greatly reduced in the treated series as compared with the controls. In the treated series, only 3 cases of vaginitis occurred in 50 cases, an incidence of 6 per cent. All were found in the proflavine group and in all the infecting organism was the *Staph. pyogenes*. It was afterwards discovered that these cases were part of a minor outbreak of staphylococcal infection which was ultimately traced to a carrier among the staff of the operating theatre. Phage typing of the staphylococci was not undertaken, as, by the time a carrier was suspected, the first strains isolated had been destroyed.

In the control group, 11 cases of vaginitis occurred in 43 cases, an incidence of 26 per cent; in 6 cases the predominating organism was the *B. proteus*.

The incidence of cystitis was identical in the two groups; in the treated group there were 15 cases of cystitis in 50 cases and in the control group 13 cases of cystitis in 43 cases, an incidence in both groups of about 30 per cent.

No record could be found of the incidence of cystitis following vaginal operations, but it is generally accepted as a common complication of gynaecological surgery. Shaw (1950) stresses the fact that care must be taken not to perform a plastic operation until the bladder is quite clean and Millin and Read (1950) recommend a short course of one of the sulphonamide drugs as a prophylactic whenever instrumentation of the urinary tract is necessary.

The incidence of cystitis was clearly not affected by the local vaginal therapy, but the antibiotics used in cases of cystitis undoubtedly influenced the vaginal flora.

Self-retaining catheters were used in all operations for the "Manchester" Fothergill repair, anterior colporrhaphy and plastic repair of urethrocele. The catheter generally stayed in place for 2-5 days, but if it fell out it was usually not re-inserted. One of the surgeons adopted the advice of Woodruff and Te Linde (1939), and instilled one ounce of 0·5 per cent mercurochrome into the bladder at the end of the operation. There is no specific record of the cases in which this technique was used, and it is thus impossible to assess the results.

In this series of cases, 21 patients complained of stress incontinence prior to operation, and 7 patients suffered from post-operative retention of urine.

A variety of therapeutic agents can be incorporated in the ethyl cellulose jelly. Three were chosen for the purpose of the present investigation. From the results obtained there appeared to be little to choose between them. Proflavine has the disadvantage of staining bedclothes. With sulphathiazole there is a risk of reaction in

a sensitive patient. This would appear to leave lactic acid jelly as the first choice for the prevention of post-operative vaginitis. Gentian violet or ichthammol and glycerine jelly might have been effective in staphylococcal vaginitis, but the staining properties of these jellies, particularly the former, prohibit their use.

Summary

(1) The effects of intra-vaginal therapy with medicated ethyl cellulose jellies after gynaecological operations have been studied.

(2) In a group of 43 control cases, the bacteriological findings following gynaecological operations were studied.

(3) The incidence of post-operative vaginitis in the control series was 11 cases out of 43, or 26 per cent.

(4) In a group of 50 patients who received treatment with medicated ethyl cellulose jellies, 3 cases of vaginitis occurred, an incidence of 6 per cent.

(5) The jellies were impregnated with proflavine 0·2 per cent or sulphathiazole 10 per cent or lactic acid 5 per cent. Lactic acid appeared to be the treatment of choice as it is non-staining and unlikely to cause any reaction due to sensitivity.

(6) The incidence of post-operative cystitis was identical in the two groups at approximately 30 per cent. Vaginal therapy is thus not effective in preventing post-operative urinary infection.

(7) The method of treatment was found to be simple in use, acceptable to the patients and free from ill-effects.

Acknowledgments

We should like to thank Miss M. E. Landau, M.D., F.R.C.S., and Miss S. G. Mocatta, M.D., F.R.C.S., M.R.C.O.G., for their co-operation in allowing us to use their patients, and Sister Booker for faithfully carrying out the post-operative treatment.

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HARDNESS AND GROWTH OF THE FOETAL HEAD

BY

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THE induction of premature labour in patients with contracted pelves was probably first practised by Louise Bourgeois (1563-1636) accoucheuse to the French Court. It is possible that Madame Bourgeois derived the idea from Ambroise Paré (1510-90) whose pupil she was, though there are no records that Paré himself ever induced premature labour for patients with contracted pelves. In this country it was not until 1756, as Denman records in his *Practice of Midwifery*, that this obstetric manœuvre met with the general approbation of the eminent men at that time. The first recorded case in this country was the wife of a linen draper in the Strand. This method of treatment became very popular in England and was referred to by Spencer as "that purely English operation".

The rationale of premature induction of labour in cases of suspected minor cephalopelvic disproportion is based on the assumptions that the foetal head gets larger as pregnancy advances and also that the head becomes harder and less able to mould as term approaches. The first of these assumptions, namely that growth of the foetal head is continuous throughout pregnancy is a common-sense belief supported by some evidence resulting from measurements. The second assumption is based purely on clinical experience and it does not seem likely that any clinician would doubt that the head becomes harder and less mouldable as the foetus gets older. The object of the work described below was to consider the significance of that growth and to discover the reason for and to express objectively the clinical observation associated with hardness and moulding.

A. HEAD GROWTH

The size of the foetal head in the biparietal, occipito-frontal and sub-occipito-bregmatic diameters was measured with calipers in 1,083 cases, the rate of growth being found by relating the size of the diameter measured to the age of the foetus as calculated from the maternal menstrual history. It was shown (Macdonald, 1953) that in the last weeks of pregnancy growth in the biparietal and occipito-frontal diameters was approximately 1 mm. a week while in the sub-occipito-bregmatic diameter growth was less, being about 0·8 mm. a week, there being no cessation of growth in any of the diameters measured. Furthermore, it was found that the diameters measured were larger in the male than in the female for corresponding lengths of gestation.

1. *Area of normal engagement of the head*

From these measurements it was possible to calculate the area bounded by the circumference having the biparietal and sub-occipito-bregmatic diameters as axes. This area is that normally presented to the birth canal and is the smallest cross-sectional area that the head can form by flexion.

The calculated area for each week of late pregnancy for each sex is represented in Fig. 1. It will be seen that there is an increase of approximately 7 sq. cm. in the size of the area of normal engagement of the head between the 36th and 40th weeks of pregnancy, an increase of about 10 per cent. This proportional increase in the normal area of engagement is the same for each sex, though the absolute measurements are greater in the male foetus. This might be due to a true sex difference or merely to smaller female birth weight.

2. *Head size and weight of the foetus*

Each of the three head diameters measured was plotted against the birth weight of the foetus

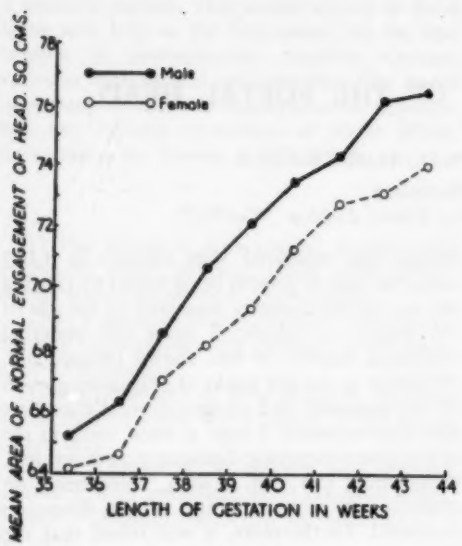

FIG. 1

Mean area of normal engagement of the foetal head plotted against length of gestation.

and it was found that with an increase in birth weight there was an increase in each of their dimensions. Furthermore, it was apparent that there was a sex difference in this data, and that for corresponding birth weights males had larger heads than females at birth.

Evidence that the size of the head is related to sex as well as to weight is shown in Table I and Fig. 2, where the area of normal engagement is plotted against birth weight for each sex. Thus the size of the head of the foetus is related to birth weight *and* to the sex of the foetus.

Ince (1939) endeavoured to assess birth weight from radiological measurements of the foetal head *in utero*. He found that this was not possible except within wide limits and it is conceivable that one of the difficulties in making this assessment is the fact that head size is related not only to birth weight, but to the sex of the foetus.

The size of the foetal head is therefore related to the age, the weight and the sex of the foetus.

B. Hardness of the Foetal Head

As little change in volume of the cranium can take place because of the incompressibility of the cranial contents, the effect of moulding must be restricted almost entirely to a change in shape. The changes in shape are possible because of the softness of the bones and the loose connexions they have with one another at the sutures. Holland (1922) described the changes which might take place in moulding as a displacement of the bones, chiefly at the junction of the plate with the base of the occipital bone, and a bending of the individual bones which compose the vault. "The greatest bending of individual bones occurs in the parietals and frontals . . . Bending of the bones is secondary to the occipital hinge movement and is a very necessary accompaniment."

Because of the part played in moulding by the bones of the cranial vault, particularly the parietals, it was decided to subject these bones to physical tests and chemical analysis in the hope that some of the factors responsible for the

TABLE I

"Engaging" Area Related to Birth Weight

Weight (ounces)	80–83		84–87		88–91		92–95		96–99		100–103		104–107		108–111	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
"Engaging" Area (sq. cm.)	62·4	63·2	62·4	62·5	65·2	64·1	65·9	64·8	67·7	66·5	69·4	68·4	70·3	69·0	70·4	69·7
Weight (ounces)	112–115		116–119		120–123		124–127		128–131		132–135		136–139		140–143	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
"Engaging" Area (sq. cm.)	71·3	70·9	73·2	71·5	74·0	72·1	74·7	72·5	75·9	73·2	77·5	75·0	76·0	74·4	76·5	76·0

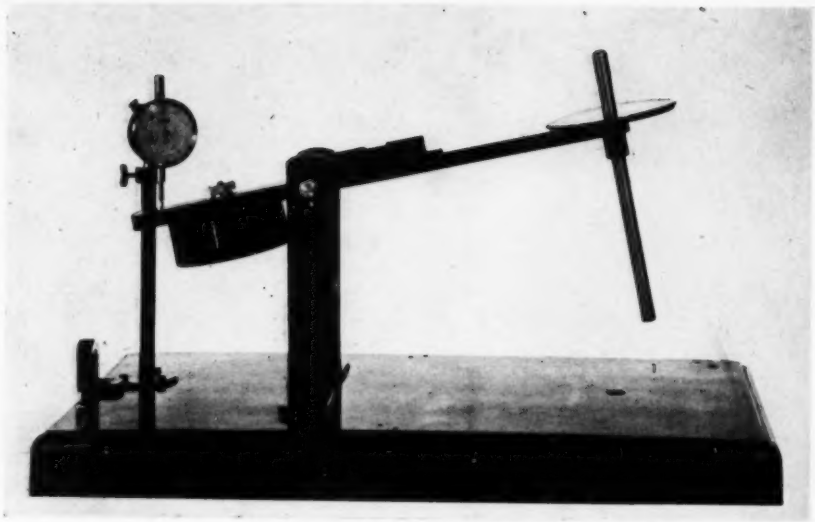

FIG. 4

The apparatus used to determine the ability of a foetal parietal bone to withstand flattening.

increasing hardness of the foetal head, as full term approaches, could be evaluated.

1. *Thickness of the foetal parietal bone*

The mean thickness of each of a series of parietal bones was obtained by measuring numerous places on each bone with a micrometer screw gauge. The mean thickness obtained from these measurements was plotted against the age of the bone (Table II and Fig. 3). It is seen that there is an increase in mean thickness of the parietal bones as the foetal age increases.

2. *Relative thickness in different regions of a parietal bone*

The inner surface of the parietal bones was marked by pencil with a series of dots about 1 cm. apart. Each dot was numbered, the numbering commencing at the periphery and proceeding in a spiral manner to the centre. If the thickness at each point was plotted against the helical number of that point, then the slope of the resultant line would show if the parietal bone altered in thickness between the centre and

TABLE II

Showing the Sex, Age and Mean Thickness of Foetal Parietal Bones

Sex	Age (weeks)	Mean Thickness ($\frac{1}{1000}$ inch)
F	24·4	21
F	24·6	16
M	28·0	31
F	30·7	17
F	31·8	27
F	32·0	22
M	32·1	11
M	33·1	23
F	34·1	20
F	36·1	22
F	37·0	29
M	37·1	29
M	38·7	32
M	39·3	21
M	39·4	29
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F	40·4	33
M	41·1	38
M	43·6	29
F	44·4	26
M	45·0	36

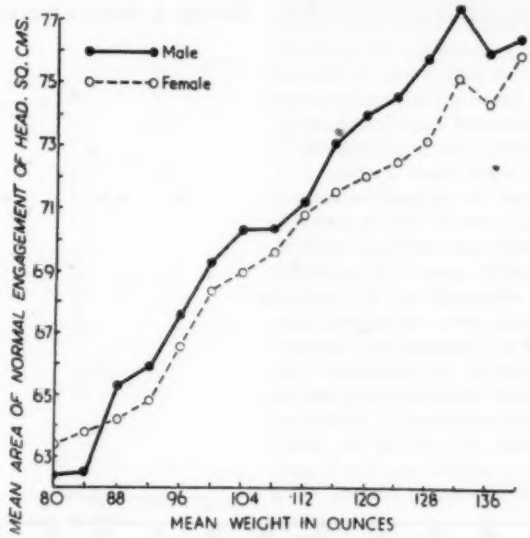

FIG. 2

Mean area of normal engagement of the foetal head plotted against birth weight.

the periphery. For example, a fitted line that sloped upwards would indicate that the periphery of the bone was thinner than the centre and vice versa.

This was done and it was found that the periphery of the parietal bone of premature foetuses was thinner than the centre and that the periphery of the bone increased in thickness at a rate greater than the centre, so that at term the parietal bone was of uniform overall thickness.

3. *The ability of the parietal bone to withstand flattening*

It was decided to compare the effects of pressure on the eminence of the parietal bones from foetuses of various ages because it was felt that in cephalo-pelvic disproportion this region would be subjected to considerable pressure.

For this the special apparatus shown in Fig. 4 was devised. This consisted of a lever with arms of unequal length balanced between two uprights with the aid of a weight. At the end of the long arm was an adjustable vertical rod, the lower end of which was made to rest on the parietal eminence. The upper end protruded above the lever and formed an axis onto which specially constructed weights could be added. The short arm of the lever had resting on its upper surface an engineer's dial test indicator, this being an instrument in which any alteration in length of its vertical antenna was recorded on a dial. This instrument was able to record movements of 0·01 mm. in the length of the antenna.

Because of its irregular outline each parietal bone, after removal of all soft tissues, was cut so that its rim formed a circle, the radius of which was 2·5 cm. from the parietal eminence. The bone was placed with its concavity downwards and the vertical rod was placed on the eminence and adjusted so that the balanced lever was horizontal. Weights of 2 pounds up to 10 pounds in half pounds were added, a reading of the dial test indicator being taken after the addition of each weight. These readings, which were repeated 3 times on each bone, gave a measurement of the amount of downward movement of the parietal eminence, and thus the response of the bone to pressure on the eminence. From these readings for each bone the mean weight in pounds required to depress the bone through a distance represented by one division

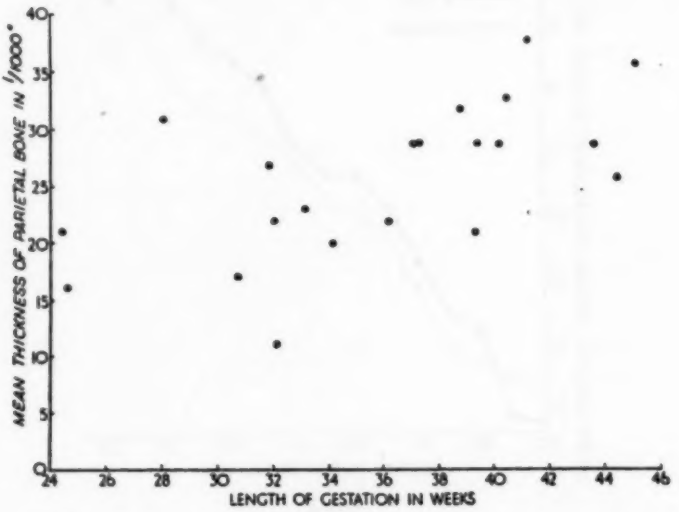

FIG. 3

Mean thickness of the parietal bone plotted against length of gestation.

on the dial test indicator was determined and these were plotted against length of gestation of the bone. Fig. 5 shows that the older the foetus the more resistant to alterations of shape is its parietal bone, when force is applied to its parietal eminence.

C. Chemical Analysis

The bones of the vault of the foetal skull were examined for the percentage content of calcium, phosphorus, carbonate and collagen (Macdonald, 1954). It was found that the proportions of calcium and carbonate present increased with the age of the foetus, while the proportions of phosphorus and collagen did not show this increase. It is thought there is an increase in the proportion and amount of calcium carbonate in the bones of the foetus as it ages and that this increasing calcification is partly responsible for the increasing hardness of the foetal head.

"Postmaturity"

It is of interest to note that all the measurements of growth and hardness made on the post-40-week foetuses showed the same plan of changes as those made on the pre-40-week foetuses. Thus the head undergoes the same degree of change between 40-44 weeks as it did between 36-40 weeks. The head of the post-40-week foetus was larger and its parietal bones were thicker, less liable to be flattened and had increased calcification compared with younger foetuses and there was *no* evidence that at 40 weeks was there a cessation or retardation of the processes making the head larger and less mouldable.

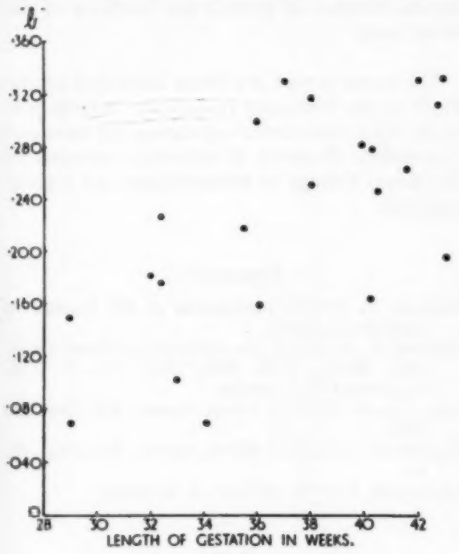

Fig. 5

Weight required ("b") to depress a foetal parietal bone a fixed distance plotted against length of gestation.

Discussion

The problem of obstruction to childbirth *per vias naturales*, in any single case, can often be resolved into two components, one, a relatively fixed quantity, the size of the maternal pelvis, and the other, an alterable quantity, the size and suppleness of the head of the foetus. That size and hardness of the foetal head alter with the age of the foetus is accepted by most as a fact and the work described assesses some of these properties of the head with particular reference to foetal age.

By measuring various diameters of the head of the new-born and comparing these findings with the length of gestation of the infant it has been possible to show that in the last few weeks of intra-uterine life the mean size of the diameters of the foetal head increases. The mean increase in the biparietal and occipito-frontal diameters is 1 mm. a week while in the sub-occipito-bregmatic diameter of the head the increase is 0·8 mm. a week. It was also shown that the size of these diameters was related to the sex and the weight of the foetus. Though the mean rate of increase of the diameters measured is known, and though the mean increase in the area of "normal engagement" of the head (bounded by the circumference having the biparietal and sub-occipito-bregmatic diameters as axes) can be calculated, it is not possible, given the age of the foetus, to predict the dimensions of its head, even if sex and weight could be determined *in utero*, because of the wide scatter about the mean value.

When the foetal head changes shape as a result of pressure applied to it by the birth canal the genesis of the altered configuration is found to

consist of two components, one which lies in the sutures of fibrous tissue which join the skull bones in a foetus, and the other in the skull bones themselves which can undergo alteration in their shape in response to pressure. The extent of the alteration with age, if any, in the flexibility of the bones along the suture lines of the skull has not been investigated. The parietal bone, as it forms approximately three-quarters of the circumference of "normal engagement", has been examined by chemical and physical means. The chemical findings showed an increase in the proportions of calcium and carbonate as the foetus gets older and the physical tests showed an increase in the thickness and in the resistance to flattening of the parietal bone as the foetus ages.

The increase in the resistance to flattening is evidence that the parietal bone is becoming "harder", whereas the increase in thickness provides one possible explanation for this increase in the hardness of the bone. Furthermore, it was found that the thickness of a parietal bone was not uniform until about term; prior to this time the bone was thickest at the centre and gradually thinned towards the periphery. Apart from any increased rigidity due to an overall thickening of the parietal bone, the rim of the bone, by becoming thicker at a rate relatively greater than the centre must, to an increasing degree as foetal age advances, act as a splint which tends to resist any deformation of the parietal bone.

Another possible factor concerned in the increasing hardness of the parietal bone as it ages is the altered chemical composition of the bone resulting in the probable deposition of an increasing amount of calcium carbonate.

Those foetuses which were delivered from 41-45 weeks after the first day of the last menstrual period showed the changes in the parietal bones and in the size of the head which were to be expected from the changes found in the younger foetuses. This is of obstetric interest in view of the uncertainty that exists regarding the properties of the head after the foetus has passed term.

Summary

(1) The growth in the foetal head in the last weeks of pregnancy is such that the area of "normal engagement" of the head increases 10 per cent in 4 weeks.

(2) The head of the male foetus is larger than that of the female for corresponding lengths of gestation and for corresponding birth weights.

(3) Tests designed to assess "hardness" of the parietal bones showed that as the foetus matures, its parietal bone increases in thickness and in its resistance to a standard deformation.

(4) The rim of the parietal bone increases in thickness at a greater rate than the centre, thereby forming a more rigid "splint" for the whole bone as pregnancy advances.

(5) There is increased calcification of the parietal and frontal bones of the foetus as it becomes older.

(6) "Postmaturity" is associated with the normal increase of growth and hardness of the foetal head.

This paper is part of a thesis submitted for the Ph.D. in the University of London. A large part of the work was carried out during the tenure of Leverhulme Research Scholarships awarded by the Royal College of Obstetricians and Gynaecologists.

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FIG. 1

Showing markings from Uterine Contraction Ring and Gangrene of legs.

REPORT ON A CASE OF IRREDUCIBLE CONSTRICTION RING

BY

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THE patient was a primigravida aged 28, who had been married for 1½ years. She had a compression fracture of the twelfth dorsal vertebra at the age of 11, but no other illness. During pregnancy she was well, except for occasional cramp. At 26 weeks she had a slight blood-staining, but this did not recur. The foetus presented by the breech, and version was unsuccessful at 32 weeks.

Labour commenced spontaneously at 36 weeks, with premature rupture of membranes. Contractions were strong and frequent from the beginning. After 24 hours the pains became colicky in nature, and were referred chiefly to both iliac fossae. The patient, in spite of sedation, became distressed. After 36 hours the os was fully dilated and the breech was showing at the vulva, but there was no advance with the contractions. The foetal heart rose to 186 and immediate delivery was essential.

Nitrous oxide, oxygen and ether anaesthetic was administered and a hand was passed inside the uterus, with the idea of bringing down a leg.

A constriction ring was immediately felt as a thick, tight band, gripping the foetus round the trunk. Both legs were fully extended, and the ring was at the level of the popliteal spaces.

Anaesthesia was deepened to try to release the ring, and amyl nitrite inhalation was also given without effect. Chloroform was then added to the anaesthetic, but there was no change in the ring.

Anaesthesia was continued for about an hour, without any improvement, and it was then decided that Caesarean section was necessary. At operation, the lower segment was thin, and the constriction ring lay at the junction of upper and lower uterine segments. It was impossible to deliver the foetus until the ring had been incised.

The infant was still-born and at first sight appeared to be macerated, but on further inspection a blue mark was seen round the body, behind the knees and round the trunk, as though a tight cord had been tied around it for some time (Fig. 1). The legs and buttocks were gangrenous, but the rest of the child was normal, with no signs of maceration.

The infant weighed 7 pounds 5 ounces.

The Caesarean wound healed by first intention and the puerperium was apyrexial.

During labour, which lasted for 36 hours, the following drugs were given: chloral gr. xxx, pethidine 100 mg., omnopon gr. ⅓, and scopolamine gr. 1/150.

TETANUS FOLLOWING COLPO-PERINEORRHAPHY

BY

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THE occurrence of tetanus following a surgical operation must always be regarded as serious. In this particular case, infection arose in an unusual way and this appears to justify the publication of a brief report.

CASE REPORT

Mrs. M. was 68 years old. She was a widow and nulliparous.

Past History. At the age of 43 she underwent subtotal hysterectomy. There had been no bleeding since then. In 1948 she had a haemorrhoidectomy.

On 19th August, 1951 she was admitted to the Elizabeth Garrett Anderson Hospital with a left inguinal hernia and procidentia for which she had worn a ring for 4 years.

Operation was performed on 23rd August, 1951 and consisted of repair of the inguinal hernia followed by a Fothergill repair for procidentia following subtotal hysterectomy.

The immediate post-operative course was satisfactory but on September 9th the patient complained of a sore throat. On 13th September she was unable to open her mouth. On examination it was found that there was marked trismus and the patient could only open her mouth one inch. There was slight *risus sardonicus*. The pelvis was clear except for slight thickening high up on the left and the wounds were healed. A swab taken from the vagina was negative for *Clostridia*. A throat swab was similarly negative. The patient was seen by Dr. Helen Dimsdale who diagnosed her condition as modified tetanus.

Treatment consisted in the administration of 100,000 units of anti-tetanic serum intravenously, after a test dose. Eight days after a further 100,000 units was given intramuscularly.

The patient made an uneventful recovery.

COMMENT

An intensive search was made for the source of infection. No *Clostridia* were isolated from the operating theatre, dust, drums and containers for catgut being examined. The remaining tubes of the batch of catgut used at the operation were sent to the manufacturers but examination was negative.

The condition of the vaginal wall at operation was very atrophic with evidence of senile vaginitis. Stilboestrol pessaries were inserted during the post-operative period with the idea of facilitating healing. These were made on the hospital premises and a batch of raw gelatine supplied for this purpose was found to contain *Clostridium tetani*. It was concluded that this was the most probable source of infection. It must be noted that gelatine used for making pessaries cannot be sterilized and that, therefore, pessaries made up in a gelatine base may possibly be dangerous, especially if used in post-operative cases. Steps are now taken to test each batch of gelatine used for making pessaries.

SUMMARY

A case is reported in which tetanus was diagnosed 21 days after operation for inguinal herniorrhaphy and colpo-perineorrhaphy. The source of infection appeared to be a gelatine base used for making up stilboestrol pessaries which were inserted into the vagina during the post-operative period.

Acknowledgment must be made to those members of the staff of the Elizabeth Garrett Anderson Hospital who were concerned in the diagnosis and treatment of this case, especially Miss A. H. Baker, F.R.C.S., Surgeon, Dr. Helen Dimsdale, F.R.C.P., Neurologist and Dr. B. J. Haram, Pathologist.

WILFRED SHAW

Obituary

WILFRED SHAW

1897–1953

WILFRED SHAW died on 9th December, 1953 at an early age and at the height of his powers. He was not yet 56 years old and suffered a very long illness before he died. His scholastic career was exceptional from the beginning; from King Edward's School at Birmingham he went to St. John's College, Cambridge, with a Foundation Scholarship and Exhibition and he won the Wrights Prize. He obtained a first class Honours in the Natural Sciences Tripos, and then came up to St. Bartholomew's Hospital, London. He had a brilliant career at the hospital both as a student and afterwards, and won the Shuter Scholarship and the Matthews Duncan Prize and Gold Medal.

He qualified in 1921 and was house surgeon to Sir Charles Gordon Watson when he began to show great promise in surgery. He became a F.R.C.S.(Eng.) in 1923 and took his M.D. at Cambridge in 1928 and was elected F.R.C.O.G. in 1932 and was a foundation member when the College was first formed. The Royal College of Obstetricians and Gynaecologists recognized his outstanding knowledge of gynaecological pathology by making him a member of the Museum Committee and the Pathology Committee.

He was a one-time examiner at the Universities of Oxford, Cambridge and London, also for the Conjoint Board and for the M.R.C.O.G. degree.

After doing his house appointments Wilfred Shaw began to study gynaecology and obstetrics in Vienna, Berlin, Gratz, Munich and Dublin. He established an association between the Frauen Kliniks in Vienna and St. Bartholomew's Hospital which has lasted until the present time. He always had a great respect for the gynaecological pathologists in Germany and Austria and kept up a correspondence with many, but in particular with Oscar Frankel, Walter Schiller and Robert Meyer.

Shaw was the first to hold the post of Resident Assistant Physician Accoucheur at St. Bartholomew's and resided for four years in a flat in the hospital. This is an appointment created under the aegis of the University of London. During the whole of this time he devoted his great energies to the study of ovarian and uterine physiology and pathology. He had an international reputation as a gynaecological pathologist and was a pioneer in the subject in this country. He began to publish a long series of papers on the following conditions—metropathia haemorrhagica, the histological changes in the uterine wall associated with multiparity, ovarian tumours, the Shaw-Dastur cells of the ovary, the anatomy of the pelvic floor, a new operation for stress incontinence and a new method of repairing pelvic floor prolapse. The Williamson Laboratory, which is endowed and forms part of the Gynaecological and Obstetrical Department, was organized and raised to a high state of efficiency by Wilfred Shaw. The hospital owes him a very great debt for his brilliant work, great example and the guidance of his junior colleagues ever since he took charge of the laboratory.

Shaw won at Cambridge in 1929 the Raymond Horton Smith Hartley Prize for the best M.D. thesis of the year, and previously he obtained the Lawrence Research Scholarship and Gold Medal and the Cattlin Research Scholarship at the hospital. In 1931 he received the Jacksonian Prize of the Royal College of Surgeons and an Arnott Demonstratorship followed.

He was elected Assistant Physician Accoucheur in 1930 and after Dr. Barris died and Dr. Donaldson retired he became Surgeon

in Charge of the department. He was gynaecologist to St. Andrew's Hospital, Dollis Hill, but soon gave up other appointments so that he could concentrate on his own teaching hospital. Even when his private practice occupied his time outside the hospital he continued to do research work on various problems for he was a relentless worker, and continued to publish papers and articles throughout his career. He was really at his happiest while doing practical work in the laboratory and each of his published papers had the stamp of individuality and originality. His exceptional memory and wide reading made him able to quote, at a moment's notice, from the international literature on his subject. His two textbooks on gynaecology and on obstetrics were an immediate success, the one on gynaecology having already reached its 5th edition. These books have a wide circulation and have reached many countries. More recently he wrote a large textbook for nurses which has also gained a well-deserved popularity. Shaw's international reputation produced a wide correspondence and he had many visitors from abroad, particularly from the European continent, America, Canada and India.

During the 1914-18 war Wilfred Shaw saw active service as a surgeon-probationer and had a good deal of experience in a destroyer. When the 1939-45 war broke out he did not join the Emergency Medical Service but was asked to take control of a Maternity Unit in Bradford-on-Avon, where he did most excellent work. The long series of cases which he had under his own care proved conclusively that in his hands the doctrine of non-intervention in obstetrics, of which he was such a protagonist, was the safer course to adopt. He was also obstetrical and gynaecological adviser to a wide area around his hospital and his work was greatly appreciated by many doctors in the neighbourhood.

Shaw's brilliant brain was not satisfied to concentrate only on his professional work. He took a great interest in astro-physics, English history and poetry, and the history of St. Bartholomew's. His students always had the benefit of his acute observation. His method of teaching was very individual and discussion was apt to range wide and far to include any subject under the sun. His memory was prodigious for he never forgot a face, either of his students or patients. He could relate the minute detail of past history in both student and patient many years after his first contact with them.

Thousands of Bart's men will continue to remember Shaw as "Wilfred" for he was always referred to by his christian name. Many legendary stories are associated with him, for his quick wit and repartee were famous.

His technical ability as a surgeon was very high indeed and his original mind was always searching for a new technique. Many came to watch him operate and his boldness under difficult circumstances was the envy of all his juniors.

But although he was so happy when working at his chosen subject Wilfred Shaw was never happier than when at home with his family around him. In later years he became fascinated with horticulture and did a great deal of fruit tree grafting which was his special interest. He quickly attained specialized knowledge about plant biology and hormonology which his restless brain applied to his hobby.

His friends will like to remember Wilfred Shaw remaining true to his ideals even during his recent illness which lasted for two years. During this time and indeed until quite recently he insisted on continuing to write and correct the proofs of his new book on operative gynaecology, which is now in the press. This book should be a memorial to Wilfred Shaw, and for those who knew him intimately it will be something else as well—it will be in memory of a man whose original thought, whose publications, whose tenacity of purpose and clear thinking have left their mark not only on those here but also upon many hundreds of Bart's men who since 1923 have been taught and guided by him.

JOHN BEATTIE

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At a meeting of the Council held in the College House on Saturday, 27th March, 1954, with the President, Mr. Arthur A. Gemmell, in the Chair,

Edward Solomons

was admitted to the Fellowship.

INTERNATIONAL CONGRESS ON GYNAECOLOGY AND OBSTETRICS, GENEVA

26th to 31st July, 1954

The Information Bulletin, describing the organization of the Congress, has been printed and can be obtained at the General Secretariat, Maternité, Geneva, or in all branches of the American Express Company.

The *main lectures* will be delivered by Professors Butenandt (Tübingen), Caspersson (Stockholm), Houssay (Buenos Aires), Oberling (Paris), Penrose (London), Sigerist (Yale and Zurich), Warkany (Cincinnati). Thirty to thirty-five eminent gynaecologists from all over the world will report on the general theme, "prophylaxis in gynaecology and obstetrics", and 100 to 120 other speakers will enlarge upon and discuss these papers.

The speakers may use one of the five *official languages* of the Congress: French, English, German, Spanish and Italian; simultaneous translation into French and English, by short waves and ear-phones, will be provided.

A programme of *60 free communications*, without translation, is being prepared.

The *scientific and technical exhibits* are meeting with great interest and numerous applications for registration have already been received.

Several *scientific films* have been registered for a first presentation and will be shown at the Congress's moving picture hall.

For further information, please apply to the Secretariat of the Congress, Maternité, Geneva, Switzerland.

REPORTS OF SOCIETIES

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

JUNE 1953

A Meeting of the North of England Obstetrical and Gynaecological Society was held in the Royal Victoria Infirmary, Newcastle upon Tyne, on Friday, 12th June, 1953, with the President, Mr. D. Currie in the Chair.

Dr. J. W. F. Scrimgeour read a record of

A CASE OF ECLAMPSIA COMPLICATED BY SEVERE HAEMATURIA

A primigravida, aged 19 years, and 38 weeks pregnant, was admitted to Crumpsall Hospital, Manchester, at 10 a.m. on the 8th December, 1952. Her husband said she had had a fit 1 hour before admission, preceded by severe headache lasting about 6 hours. Booked for hospital confinement on social grounds, her antenatal care had been supervised by a local authority clinic, where at no time had the blood-pressure been raised; nor had there been other signs of pre-eclampsia, until the onset of the headache before admission.

When seen the patient was complaining of severe headache, and was drowsy and incoherent with stertorous respirations. There was marked oedema of the face and ankles. The blood-pressure was 160/130. The foetus corresponded in size with the period of gestation and was presenting as a vertex which was not engaged in the pelvis; the foetal heart was normal.

Six ounces of urine obtained by catheter boiled solid, and on microscopic examination contained scanty granular casts and leucocytes with no R.B.C.s and no organisms. The routine treatment in the unit for eclampsia was instituted—sedation with morphia and chloral hydrate, intramuscular magnesium sulphate, and nursing in a darkened ward, etc.

During the next 24 hours the patient's condition showed no deterioration. There were no further fits and the headache had disappeared. The blood-pressure remained at about the same level. The urinary output during this period was 14 ounces and still boiled solid with albumen. The intake during the same period was 30 ounces. Thirty-one hours after admission 3 ounces of urine were obtained which were found to be heavily blood stained. The blood-pressure was then 150/120 and, as the patient was again complaining of headache, 50 ml. of hypertonic sucrose (50 per cent) were given intravenously. Four hours later a further 2 ounces of urine were obtained resembling almost pure blood, and microscopy confirmed the presence of very large numbers of R.B.C. The urine was sterile. Biochemical tests showed that the

serum urea was 65 mg./100 ml. (raised); the
serum sodium was 322 mg./100 ml. (normal); the
serum potassium was 23·4 mg./100 ml. (very slightly raised);
serum chlorides were 604 mg./100 ml. (normal); and the
serum proteins were 6·5 per cent with an A./G. ratio of 1·2 : 1.

It was felt that the severe degree of haematuria associated with marked oliguria was strongly suggestive of the onset of bilateral renal cortical necrosis. As the prognosis of this condition depended on whether the metabolism could be maintained by means of a "Bull diet" regime, to allow of spontaneous renal regeneration, and as the causative factor was still present, namely an acute toxaemia with a living foetus, it seemed logical to terminate the pregnancy immediately.

With the head not engaged at 38 weeks, a speedy response to the surgical induction of labour seemed unlikely. Vaginal examination was performed in the theatre under general anaesthesia, the intention being to perform a Caesarean section unless the cervix was found to be completely taken up and beginning to dilate. As the cervix was tightly closed and not taken up at all, lower segment Caesarean section was carried out, a living male infant weighing 6 pounds 14 ounces being delivered. The uterus was particularly inspected for evidence of haemorrhagic areas or retro-placental clot, neither being found.

By 10 a.m. on the morning after the operation the patient had a moderate diuresis, the urine being clear and containing only a few R.B.C., and within the next 24 hours a total of 27 ounces of urine were secreted, which at the end of this period was normal on microscopic examination. The urinary output remained high, and on the 2nd post-operative day the serum urea had fallen to 25 mg./100 ml.

The patient's further progress was uneventful apart from a mild iron deficiency anaemia. She was, however, kept in hospital for 3 weeks, when the blood-pressure was 110/80 and the urine was normal. Renal function tests including intravenous pyelography revealed no abnormality.

Six weeks after discharge the tests were again normal. The patient has not reported back again although requested.

An accurate diagnosis of the pathology responsible for the haematuria in this patient did not seem possible. By reason of the rapid recovery of renal function and the apparent lack of any residual signs, the pre-operative presumptive diagnosis of bilateral renal cortical necrosis could be excluded although a localized infarct with the same aetiology would appear to be the most probable answer. A focal nephritis was also a possibility. Bleeding from veins in the renal pelvis or bladder had also been considered, but the association with severe oliguria, and the prompt recovery from haematuria were against this diagnosis. The last condition which was considered was bleeding due to a fibrinolysin in the blood, a complication which had been met with in a case of toxaemia several months before, but the absence of any bleeding tendency

during operation would appear to exclude it. This point was only considered in retrospect and the blood picture was not investigated from this aspect.

Particular interest in the case was first aroused by the fact that none of the medical staff at Crumpsall Hospital had ever seen a case of eclampsia complicated by haematuria, and since then many obstetricians of great experience had denied ever having encountered such a case. In the standard text-book the question was invariably dismissed by such a phrase as "haematuria may be present in severe cases", some text-books even giving the impression that haematuria was a usual complication of eclampsia. Dieckmann, in his monograph "The Toxaemias of Pregnancy" stated that microscopic haematuria was common, and that severe haematuria occurred in 2 per cent of cases; he did not, however, enlarge on this statement or support it in any way.

Dr. Scrimgeour concluded that he had not been able to find any recent references to the complication and it seemed surprising that such a dramatic symptom as haematuria was dealt with in such a cursory fashion, if indeed it were as frequent an occurrence as the text-books suggested.

Discussion

Dr. J. B. Cochrane asked if it was not possible that the bladder might have been damaged during catheterization, and if cystoscopy would not have been of assistance in excluding bleeding from the bladder wall.

Dr. R. Newton thought that it was strange that this condition was so rarely seen. He thought renal infarction was the most likely cause. He made a plea for the more frequent use of Caesarean section in the interests of the baby in cases of eclampsia.

Mr. D. Currie thought it difficult to determine the source of such haemorrhage and said that he had seen cases similar to the one described.

Dr. Scrimgeour, in reply, said that a rubber self-retaining catheter had been used in this case and he thought that the rapid recovery suggested that the cause was not bladder trauma.

Mr. J. B. Cochrane read a record of a case of

HYSTERECTOMY IN A YOUNG FEMALE FOR UTERINE FIBROIDS

This case, said Mr. Cochrane, presented several unusual features and a somewhat chastening end-result.

A single nulliparous woman of 24 was referred by her family doctor on account of a large mass in her lower abdomen which he diagnosed as multiple uterine fibroids. Since her menarche at 11 years of age, she always had had dysmenorrhoea, which lately had become increasingly more severe. Her menses had never been regular, varying from 28-42 days in their frequency, and lasting 2 days only, the loss always being scanty.

Examination showed a multinodular mass of fibroids corresponding in size to a 28-weeks gestation, but of a softer consistency than usually encountered in such tumours. She was otherwise healthy and had no anaemia.

Operation. At laparotomy the uterus was found so grossly distorted by many large fibroids that it was difficult to trace any recognizable outlines, and, in addition, large tortuous blood-vessels coursed over the tumour mass, mainly on the anterior and lateral aspects. There were no adhesions on the tumour surface, which was very much softer than expected, and so vascular as almost to be pulsatile. Both ovaries were uniformly enlarged, measuring 3 by 4 by 2¾ inches, were very oedematous, and contained numerous small follicular cysts.

The intended myomectomy was technically out of the question, and a hysterectomy had to be carried out. Both ovaries, however, were conserved, a wedge-shaped biopsy from one being taken for histological examination. The patient made an uninterrupted recovery, and when seen for follow-up examination 6 weeks later, her wound was well healed and both ovaries were considerably reduced in size, though still slightly larger than normal.

Specimen. The tumour mass weighed 5 pounds and representative sections showed histologically the typical pattern of fibromyomata, no evidence of sarcomatous changes being seen. The ovarian biopsy showed nothing more than simple follicular cyst formation.

The unusual features were, commented Mr. Cochrane, firstly the youth of the patient. Davids of New York, in 1952, however, reporting on 1,150 myomectomies in the past 30 years, found an incidence of 7·2 per cent of fibroids occurring in the age group of 18-25 years. Secondly the large size of the tumour mass, and its rapid growth over a presumably short space of time was noteworthy. Thirdly the absence of menorrhagia, indeed the scantiness of her menstrual loss, was remarkable, although this was noted by Davids in the case of the 18-year old girl with a huge single fibroid weighing 5 pounds 6 ounces.

Finally, the failure technically, despite the best will in the world, to undertake an operation to rid her of the fibroids and save her uterus.

Discussion

Professor Farquhar Murray had carried out multiple myomectomy in a patient in her early twenties with a large mass of fibroids. He had left a very large deformed uterus after this operation but the patient had fallen pregnant and had had her first baby some years later.

Dr. W. Hunter drew attention to the difficulty in excluding sarcomatous change in cases of uterine fibroids in young patients.

Mr. D. Currie suggested that Mr. Cochrane should follow up his patient very carefully, and besides noting that she was still alive and in good health, should record any menopausal symptoms and the age at which they arose.

Dr. J. K. Russell and Dr. G. A. Neligan read a short paper on

BLOOD LOSS FROM FOETAL CIRCULATION. A HAZARD OF LOWER SEGMENT CAESAREAN SECTION IN CASES OF PLACENTA PRAEVIA

(This article appears on page 206 of this issue)

Discussion

Dr. R. Newton said that he practised the lower segment operation in cases of placenta praevia and asked if

demonstration of the placenta by X-ray prior to operation would be of assistance in deciding the operative technique. Scott Russell had recommended tearing the uterine wall from a stab incision in the lower segment.

Mr. B. Williams described a case of vasa praevia in which an exsanguinated baby was delivered and was successfully treated by blood transfusion. He did not believe there was any safe way to make a lower segment incision in such cases and thought there was much to be said in favour of incising the upper segment followed by an easier and quicker delivery. If the placenta was posterior the lower segment operation could be carried out and if anterior the incision could be extended into the upper segment.

Professor Farquhar Murray thought the use of the lower segment operation was asking for trouble and was risky for both the baby and mother. He advocated classical Caesarean section and remarked that, in many cases, the placenta was elongated. He did not approve the immediate clamping of the cord in the absence of placenta praevia. He asked why transfusion had been delayed in the resuscitation of some of the babies and reminded the Society that many babies in cases of placenta praevia were weakly owing to prematurity and placental separation.

Dr. W. Hunter used the lower segment operation and deprecated incision of the junction between the upper and lower segments. In cases of anterior placenta praevia it was not unusual to find the greater part of the placenta lying in the upper segment where it was equally exposed to damage during Caesarean section if the upper segment was incised. On rare occasions in cases of vasa praevia it was possible and advisable to clamp a large foetal vessel through a lower segment incision before rupture of the membranes.

Dr. F. L. A. Vernon asked what anaesthetic was used for Caesarean section in cases of placenta praevia. He thought that, in view of the risk of depressing the foetal respiratory system by a general anaesthetic, spinal anaesthesia seemed to have definite advantages.

Dr. H. Doberman preferred the lower segment operation. He considered the risk of ruptured uterus was greater after classical Caesarean section when the placenta had been anterior.

Dr. D. Court asked if this observation was something new or was it something old which had been rediscovered? He considered that a new precision was now required in dealing with the baby.

Mr. D. Currie could not think of a single case in Leeds in the past 24 years in which foetal blood loss at birth had required transfusion. He asked if Dr. Russell and Dr. Neligan could show the comparative mortality rates in a series in which no blood had been given.

Dr. Russell in reply said that routine X-ray localization of the placenta had been carried out whenever possible in the past 9 months. He did not advise incision through the junction of the segments as these incisions were difficult to suture efficiently and more likely to rupture in subsequent pregnancies. The risk of striking an anterior placenta in upper segment Caesarean section was considerable. The cord was clamped quickly only when there was a rise of foetal blood loss. He would never use a spinal anaesthetic for Caesarean section in a case of placenta praevia. He preferred a general anaesthetic with gas, oxygen and ether. The comparative infant mortality figures were not known but the paediatricians assured him that the babies handled were now giving rise to less anxiety.

Dr. Neligan said that he regretted the delay in transfusing 2 babies in the series with unfortunate results but now fully appreciated the urgency of the matter.

Mr. T. Robinson read a short paper on

Routine Manual Delivery of the Placenta Following Operative Vaginal Delivery

From early recorded times, said Mr. Robinson, the potential dangers of the 3rd stage of labour had been recognized by practitioners of the obstetric art.

In 1609 Guillemeau the French King's Chirurgeon in Ordinary, a pupil of Ambroise Paré, wrote a book entitled "Childbirth or the Happy Delivery of Women", a translation of which was published in London by Hatfield in 1635. Of the third stage of labour Guillemeau said: "Either that the Quicke thrust forth the dead, or that the dead kill the Quicke." By "Quicke" he meant the parturient woman, and "the dead" referred to the placenta.

In 1949 at the 12th British Congress of Obstetrics and Gynaecology Gilliatt said that obstetricians were uneasy in their minds about the management of the third stage, and were not satisfied with the method usually written and taught.

Gilliatt was speaking of the management of the third stage in general, whereas this paper would deal only with the delivery of the placenta after operative completion of the second stage. In the modern obstetrical text-book, the account of an operative vaginal delivery ended with the delivery of the child, and yet both the indication for operation and the anaesthetic necessary for its performance had an effect, often profound, on the separation and delivery of the placenta. In spite of this, the method of delivery of the placenta was neither written nor taught. In short, only half an operation was described.

Mr. Robinson then read extracts from the records of 2 cases of chloroform poisoning described in the *British Medical Journal* (Lunt, 1953): "A manual rotation and forceps extraction for a right occipito-posterior presentation after 28 hours labour had been carried out under chloroform anaesthesia, the duration of which was approximately 20 minutes. Two hours later chloroform anaesthesia was again used for manual removal of the placenta."

"After 26 hours labour, twin males were delivered, the first by a forceps extraction, and the second by breech extraction. The patient was under chloroform anaesthesia for approximately 25 minutes. Four and a quarter hours later, chloroform was again administered, and manual removal of the placenta was performed."

In quoting these 2 cases it was not his purpose to suggest that manual delivery of the placenta would have saved these women from chloroform poisoning (although

this might well be) but to show that these 2 patients required a second anaesthetic and operation to complete their delivery. In the intervening hours between these operations they were left, as it were, on the edge of a precipice. Guillemeau might well have called this "the unhappy delivery of women", and Gilliatt's observation that obstetricians were uneasy in their minds about such matters was certainly true.

Mr. Robinson contended that manual delivery of the placenta immediately following operative delivery of the foetus under general anaesthesia ought to be considered as part of one operation, and that, except in exceptional circumstances, no woman should be allowed to come round from her anaesthetic incompletely delivered. He had found manual delivery of the placenta a certain and very satisfactory means of accomplishing this objective. Manual delivery was not synonymous with manual removal of the placenta, but was a term he had coined some years before to describe a method of delivering the placenta following breech extraction under general anaesthesia. The technique was as follows:

Immediately after the completion of the second stage, the hand, clothed in an elbow-length glove, was passed up into the lax amniotic sac so that the palm came to lie against the foetal surface of the placenta, where it rested until the uterus, aided by intravenous injection of 0·5 mg. ergometrine, expelled the placenta along with the hand and arm of the operator. The procedure was, in effect, an extension of the practice of giving ergometrine immediately after the birth of the anterior shoulder in a vertex delivery, the hand and forearm of the operator taking the place of the foetal torso in keeping open the lower uterine segment and birth canal. He had first started employing this manœuvre as a means of delivering the placenta following breech extraction, but the completeness of the control obtained by the operator over the behaviour of the uterus and the certainty of the method had led him to adopt it in all major operative vaginal deliveries under general anaesthesia.

It was not manual removal of the placenta, but, if circumstances arose while the operator was waiting for the placenta to separate, to make this operation desirable, manual removal could be carried out forthwith without loss of time or maternal blood. With the hand already in contact with the placenta, manual removal then became a very simple operation.

Mr. Robinson said that he had been practising this benign procedure for the past 5 years without any consequent mortality and with little morbidity.

Manual delivery of the placenta was not, *per se*, regarded as an indication for prophylactic chemotherapy which was used only in cases where other circumstances indicated their employment.

In carrying out routine manual delivery of the placenta it was recognized that most placentae so delivered would have been delivered safely by other means, but, in the type of case under consideration, third stage difficulties were notoriously frequent, and it was the virtual elimination of the difficulties which justified the routine employment of this benign procedure.

In 1948 Sheehan, in observations based on both clinical study and post-mortem examinations of 147 subjects of shock related to labour, found that in 30 cases in which the placenta was retained for from 2 to 8 hours, and in which haemorrhage was reported as slight, the cause of death was shock. He further stated that not one death was due to manual removal of the placenta in the first hour however vigorous the manner of removal. His own experience in carrying out manual delivery of the placenta was in accord with Sheehan's views, but vigour was never necessary in normal delivery, for the open os offered no resistance to the insertion of the hand, and manual delivery of the placenta under these circumstances was far simpler than manual removal of the placenta from the contracted uterus after attempts at expression and/or the exhibition of oxytocic drugs had failed. Further, as the hand was passed inside the lax amniotic sac no harm need follow even if infection were carried into the amniotic sac by the hand. Manual delivery of the placenta, concluded Mr. Robinson, was part of the same operation as that undertaken for the delivery of the child just as in Caesarean section it was illogical for the practitioner having embarked on delivery by operation not to complete the delivery of his patient at one and the same operation.

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Discussion

Mr. D. Currie advised completion of the third stage before the anaesthetic was discontinued after forceps or breech delivery. This was also of assistance in suturing the episiotomy incision. However, he disagreed with the method of removal as most placentas could be delivered by traction on the cord and fundal manipulation.

Professor Farquhar Murray had practised manual removal of the placenta after forceps delivery, internal version and sometimes after breech delivery for many years without regret. Exploration of the uterus also reassured him that no placental tissue was retained and that the uterine wall was intact.

Dr. R. Newton recalled that the late Dr. Daniel Dougal always removed the placenta manually when he conducted a difficult delivery.

Dr. J. M. King thought it a good thing to avoid the introduction of the hand into the uterus and advocated the use of intravenous ergometrine with the birth of the anterior shoulder.

Dr. F. L. A. Vernon said that it was safer to introduce the hand into the uterus than to leave a shocked patient to face a delayed operative removal of the placenta. He thought the dangers of early intervention had been exaggerated.

Mr. T. Robinson, in reply, said that there was no trunk to keep the birth canal open in breech cases. There was a distinct difference between manual delivery and manual removal of the placenta. After the birth he introduced his

hand into the lax uterus within the amniotic sac and placed it against the foetal surface of the placenta. The anaesthetist injected 0·5 mg. ergometrine intravenously and the placenta and hand were expelled together when the uterus contracted. If necessary he would sometimes lift out the placenta or even deliver it by cord traction.

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

October 1953

A meeting of the North of England Obstetrical and Gynaecological Society was held in Manchester on Friday, 30th October, 1953. The President, Mr. D. W. Currie took the chair at the meeting, which was devoted to a discussion on "The Management of Infertility".

Professor T. N. A. Jeffcoate delivered the opening paper. (This article appears on page 181 of this issue.)

Dr. J. K. Russell contributed a short paper on

Male Factors in Infertility

There were, he said, two particular aspects of the management of cases of infertility (to be discussed), both dealing with the assessment of the responsibility of the husband for delay in conception.

First, it was the common but unsatisfactory practice for the gynaecologist to refer husbands, unseen, for semen analysis to a colleague, generally a pathologist or urologist who was not in a position to see the problem as a whole. Many people believed that the investigation of the male was outside the province of the gynaecologist, but the problem of infertility affected husband and wife and the principle of having one experienced clinician take an active part in the investigation of both partners had much to commend it. This was not to suggest that the gynaecologist undertake semen analysis, which might be carried out by a technician, but the gynaecologist who was known to the husband and had discussed matters with him, was in a much better position to advise the couple on their problem.

His second point concerned the actual assessment of the husband's responsibility for the delay in conception. Before offering an opinion on this matter, it was surely important to have information about the fertile male yet no one, in this country at least, had made a detailed study of husbands who had shown themselves capable of fertilizing their wives repeatedly and successfully over a period of several years. Most of the work in regard to the male had been carried out on men referred to subfertility clinics, that is, on potentially subfertile men. Since 1946 he had studied husbands whose wives had had 4 or more successful pregnancies at short intervals. If these men had a problem, then it was quite the opposite of infertility, for they sought advice on how to limit the size of their families. Their physique, nutritional state, past medical history and semen quality were noted, and he would present details of the spermatozoön counts of 72 such men.

None of these men had had an illness for 3 months prior to their examination and in each case a period of at least 4 days continence was stipulated before they produced a specimen of semen for analysis. The lowest count among the 72 men was 53,000,000 per c.cm. and most were very much higher. Four of the 5 men whose counts were below 60,000,000 per c.cm. produced a number of specimens at fortnightly intervals and in no case did the count at any time fall below the level of 50,000,000 per c.cm. Statistically it was a reasonable assumption that, if a man was to achieve the reproductive performance of these 72 men, that is, if he was to fertilize his wife repeatedly and successfully over a period of several years, then it was most unlikely that his sperm count would fall below 50,000,000 per c.cm. This assumption was at variance with the finding of MacLeod and Gold (1951) who, after a study of spermatozoön density in 1,000 fertile men, concluded that the critical sperm density was 20,000,000 per c.cm. and that a man's chances of fertilizing his wife did not improve as the count rose above this level. These authors, however, used a loose definition of fertility and admitted that a number of the men they examined had experienced difficulty in fertilizing their wives. This illustrated the confusion which still existed between the quality of semen which will effect conception, perhaps after years of delay, and the quality necessary for repeated successful pregnancies at short intervals.

In applying this work to the management of the husband's investigation Dr. Russell therefore suggested that 3 or 4 semen specimens should be obtained under standard conditions from each husband, and if the count were consistently above the level of 50,000,000 per c.cm. then, so far as spermatozoön density was concerned, that man was unlikely to be responsible for delay in conception.

In summary there was a need for the gynaecologist to take a more active interest in the investigation of male infertility, and, secondly, there was a very obvious need for much more careful and extensive study of the fertile male before any reliable assessment of the fertility of men referred to subfertility clinics could be made.

REFERENCE

MacLeod, J., and Gold, R. Z. (1951): *Fertil. & Steril.*, **2**, 187.

Mr. R. H. Abbas discussed

The Value of Hysterosalpingography in Infertility

Mr. Abbas reviewed 52 hysterosalpingographies which he had performed in the previous 9 months. In broad outline, the results were as follows: 26 films showed normal internal genitalia, 21 revealed bilateral tubal occlusion, and 5 unilateral tubal obstruction. Eight showed uterine abnormalities such as fibroids, uterine filling defects, endometrial irregularities, and double uterus. In 5 films ampullary tubal dilatation was observed and in all these, impaired but definite peritoneal spill occurred, demonstrating typical appearances of tubal atony. One film showed bilateral hydrosalpinx and another the appearance we have come to recognize as pointing to a diagnosis of bilateral tuberculous pyosalpinx.

Apart from 3 cases developing vasovagal reactions and the occasional complaint of lower abdominal discomfort during the test no immediate complications were observed.

His technique was as follows. The patient was instructed to attend 10 to 15 days from the beginning of her last menstrual period. Pethidine 50 mg. by mouth was given 30-45 minutes prior to the test in nervous patients, those in whom cornual spasm was suspected and those having repeat tests. After preliminary vaginal examination the direction of the utero-cervical canal was ascertained, and care was exercised to ensure that the cannula and contrast medium are warm. Viskiosol Six (an aqueous solution of 50 per cent diodene with 6 per cent polyvinyl alcohol) was the medium used and screening was employed in every case. Usually 4 films were taken. The first after administration of 5 c.cm. of the medium, the second in half a minute from the injection of 8-10 c.cm., the remaining 2 films at 3 and 8 minutes interval.

Mr. Abbas then described in detail 7 cases of special interest.

Mr. P. Malpas drew a distinction between tests to be performed in the routine practice of gynaecology and special investigations to be carried out as part of research work. He therefore deprecated the general establishment of special sterility clinics. He too emphasized the importance of not allocating the responsibility for infertility between the partners. There was much still to be discovered—he was not satisfied that the time of ovulation could be determined accurately; little was known of the mechanism whereby the ovum was transferred to the tube; spasm was a meaningless term. The cynic might see no point in seminal analysis, for, if the standard was low, nothing could be done, and, if it was high, nothing need be done. He found it difficult to believe published figures on successful results of salpingostomy; except where the obstruction was due to post appendicitis adhesions, results were disappointing, which was not surprising for the condition of the tubal mucosa and its cilia was a more important factor than its patency.

Dr. B. Sandler discussed the importance of normal cervical mucus for conception. Some carbohydrate was essential for sperm penetration and survival in cervical mucus. The effects of cervical infection on sperm penetration varied with the causative organism. Standards were required for what was to be considered normal cervical mucus. Similarly the characters of normal semen were undefined. Personally he believed that too much importance was attached to sperm density and too little to motility and viability. Finally, the assessment to be made was of the couple, not of the individual.

Mr. Linton Snaith delivered a paper on

The Value of Infertility Work to the Patient and to the Gynaecologist

The vast majority of patients, said Mr. Snaith, fell into three categories. First there were those who attended merely for reassurance, often after a relatively short marriage, just to make sure that there was nothing wrong. The second larger group came because they were still childless after having given a reasonable chance to nature; they wanted full investigation and any treatment reasonably practicable. The third group, the most pitiful of all, were those who had been here, there and everywhere, having had a partial investigation in one place, an opinion elsewhere, and who finally came along desperately hoping that something could be suggested which would perform the magic trick; they wanted a final opinion.

The value of anything one could do differed from group to group. In the first group all that was wanted was a little sensible advice based on a careful examination and sympathetic consideration of a problem which to the patient appeared considerable. Only reassurance was required here unless there were some presenting abnormalities either in history or on examination; no treatment and no further investigations were needed. However, the couple should not be dismissed too lightly; the woman should be examined; in some cases the husband should be examined; usually it was desirable to carry out a post-coital test. The appointment should be arranged to coincide roughly with the mid-menstruum; if coitus took place before attendance it would save a second journey. If all was reasonably normal the patient should not be dismissed with a statement that "everything is all right", but one should say "come back in a year's time if nothing has happened by then, come back sooner if you think you are pregnant".

The largest number of patients fell into the second group. They had given a fair trial to nature and they wanted a proper assessment. Unless need for further treatment or longer supervision became evident, the course of investigation should be short, since a study of the records of people who have been attending for some time indicated that one rarely made any progress after the first 6 months or so of attendance. Recently they had carried out careful statistical analysis of the results of their infertility clinic over the past 10 years and had found that about 20 per cent of the patients who attended had become pregnant, a rather lower figure than usually quoted.

Analysis of what had been done with those patients was revealing. Of those in whom there had been dyspareunia or sex difficulties of one kind or another over 30 per cent became pregnant. In those who had received insufflation there were about 20 per cent of pregnancies which might reasonably be attributed to the insufflation, according to the rules laid down by Rubin. Amongst those who had hormones there were about 20 per cent in whom the pregnancy might be attributed to that treatment. Of those who had merely attended and been examined, perhaps including a post-coital test or the passage of a uterine sound, about 20 per cent conceived. In fact, this 20 per cent figure recurred with extraordinary persistence and Dr. Barns and he concluded that whatever one did with the patient it was very likely that 20 per cent would become pregnant. There was therefore every justification for a short period of investigation occupying not more than 2 or at most 3 attendances—allowing for an extra attendance for a post-coital test—permitting some treat-

ment to be advised or carried out for any evident abnormality, but not encouraging attendance for longer than 6 months in all.

They had calculated that after one year of infertility the chances of conception within the next 2 years were about 40 to 50 per cent, after 2 years infertility about 30 per cent, after 3 to 4 years 24 per cent and after 5 or more years 18 per cent, regardless of treatment and always providing that there was no manifest pathological condition.

In regard to the third category, those with the last hope attitude, one was faced with the decision very often as to whether one should carry out some treatment, possibly even salpingostomy, which offered very little prospect of success but which had not as yet been tried. These cases were the most interesting philosophically, but the least interesting medically, using the term rather narrowly and implying that the cases offered little scope for medical treatment. One had to spend some little time collecting together the information about previous investigations and then perhaps repeat some of them. One then had to decide whether to investigate these cases again, but usually these people were fairly intelligent and after frank discussion would decide for themselves. Again the value to the patient was very often one of reassurance that nothing more could be done and that they might as well accept the position, but the reassurance was nevertheless extremely valuable.

Turning to the value to the gynaecologist, Mr. Snaith recalled that when he was a house surgeon he had formed the impression that sterility was a matter of blocked tubes or misplacements of the uterus and that one carried out a D. & C. and an insufflation with air and that most patients became pregnant after this especially if they had retroversions which one could put right. As he learnt a little more about gynaecology and moved about a bit, he had found that that was the general attitude of the gynaecologist towards infertility. There were, of course, a few outstanding individuals who had some really sound ideas about the matter, and fewer still who realized how very unsatisfactory the position was and how little was known about it. Some people were even interested in the part the male had to play in fertility.

This attitude was fairly general 20 years ago and it was unfortunate that around about the same time the public began to find that they could not get very far with the average gynaecologist. Also a number of people who were not gynaecologists became aware of the very serious gap there was in gynaecological clinics, as far as the sterile patient was concerned. Many of these people were thoughtful and well meaning and often highly trained in one branch or other of medicine or physiology or biochemistry, and these "non-gynaecologists" started investigating infertility but each one tackled it from the point of view of his own particular speciality. Even worse there were some, less well meaning, not less intelligent, not less capable in their own way, certainly no less far-seeing in their perception of the inadequacy of the gynaecologists, who started off what had become, at least in the eyes of some, rather a "racket" in infertility. The others, the well meaning individuals, got together and they were joined by a few gynaecologists. In the first place this group of people had an association with a Society called The Family Planning Association, but this had formerly been the British Birth Control Association. This was an unsatisfactory connexion, being suspect by many people, some on religious grounds, others on ethical grounds and others simply because the Society was not a gynaecological one. That group of people started having annual meetings at which there were presented and discussed various papers, at first largely clinical and later more scientific. Out of these meetings developed the idea of a Society for the Study of Sub-Fertility, a Society which would be divorced from any other body, a Society which would exist for the purpose of getting together those who were interested in infertility work. That Society had now been in existence for the past 3 or 4 years and a list of the papers presented at the more recent meetings made impressive reading. It was a sad fact, however, that there were still very few proper gynaecologists associated with this Society, which was a very serious reflection upon either the gynaecological world's interest in infertility or the understanding by the gynaecological world of the real nature of the Society for the Study of Sub-Fertility.

He had been present at the first World Congress on Infertility held in New York in 1953. A number of the papers presented were of very doubtful value, but there were some extremely good papers. Nearly 1,400 people attended the conference including some of the most reputable of American gynaecologists, and the South American countries were represented by very large gatherings. The meeting did not reassure him that there was not still something of a "racket" in infertility work, but he did learn the reassuring fact that despite the element of "racket" there was quite a good deal of value and also a good deal of interest to the gynaecologist.

Mr. Snaith remarked how often one found and treated pelvic pathology, not necessarily with a resulting cure of infertility, in the course of investigation of a sterile couple. One also learned quite a good deal about the variations to be found in the pelvic organs in the normal woman. One learned how genuine an interest there may be in having children amongst the illiterate, unintelligent, dull section of the community, the poverty stricken, and how genuine their pleasure was if their desires were gratified. One learned how such patients, unintelligent, ill-educated, living in poor circumstances, how carefully and intelligently they could co-operate in investigation. One found a lot of very pleasant people, one found a lot of very annoying people.

The whole subject was frustrating but continual frustration encouraged patience and tolerance. In some ways infertility work was a kind of specialized general practice. You were dealing with a woman, better still with a couple, who had no real complaint in the medical sense of the word; they had a problem, sometimes a sex problem, sometimes a psychological problem, sometimes a truly medical problem not apparent to the patient. You developed a different attitude towards the patient. You did not have a patient with a diagnosis attached, possibly right, possibly wrong, prepared for an operation. You

had somebody who had to be handled differently and that different handling was, he believed, of inestimable value to the younger gynaecologist.

Infertility investigations and treatment were not everyone's métier. Some very sound gynaecologists and obstetricians should refuse to see infertility patients because temperamentally they were not suited to infertility work. This problem demanded a different approach from that applying to the majority of patients attending a gynaecological clinic. They should take a wider view of the whole subject of infertility, they should preserve an open mind and look on the patient, as indeed all patients, as individuals with a *problem* not as cases of disease.

There was also, concluded Mr. Snaith, an obstetrical aspect to infertility work. For example there was a higher incidence of toxaemia and of inertia, in the woman previously infertile. Apart from anything else there was an especial gratitude on the part of the patient who succeeded in producing a baby after a long period of failure. Whether or not her success was due in any part to medical intervention was of no importance. You found that you know your patient a good deal better than was usual under the conditions of specialized gynaecology and obstetrics. You would in fact, have at least a share in the satisfaction which the general practitioner experiences when one of his lifelong patients recovered from a serious illness.

Mr. F. Stabler discussed

THE EVOLUTION OF THE MANAGEMENT OF INFERTILITY

When he began gynaecology, all that was ever done was to dilate the cervix uteri and many women conceived thereafter. Then came the Rubin's test and now a woman could be pronounced barren with some certainty—although it rather shook our complacency when women conceived after we had proved their tubes to be sealed, but we now have excuses for that. Next came salpingography and more certain demonstration of where and to what degree tubes were sealed. With the elucidation of male and female hormones a bright day dawned, for now we could control ovulation and spermatogenesis, we could make imperfectly developed uteruses come to maturity and we could grow decidua where none had been before—or so we thought. Then came the discovery of what a large part genital tuberculosis played in infertility in women. Finally, with the realization that the male partner was often at fault, came the scientific investigation of the sperm—its quantity and its quality and the ability of the sperms to penetrate cervical mucus. Testicular biopsy might reveal the extent and the causation of male fertility. So we advanced a long way from the haphazard fiddling with the cervix that we did 25 years ago—or had we?

Infertility clinics were established. A clinic was a cheap way of getting a medical problem dealt with. It was suddenly realized that certain groups of clinical conditions crowded the outpatient department to the exclusion of more interesting pathological material—vaginal discharges suffered the same fate. These cases were therefore transferred to a special clinic, under the care of an aspiring young man or woman who wanted to impress that this was good work he was doing. He read all the work of the research workers and applied it. After a while he had some statistics and he published an article to show what good, thorough and up to date work he did. His rivals went one better and did even more at their clinics and published articles that hinted that it was almost criminal to fail to carry out as many and as drastic tests as they did. The seniors caught the infection and for fear of seeming old fashioned they took to practising the new regime.

But what of the patient? She had come not to find out how barren she was, nor why she was barren, nor to have treatment for some condition which she did not know was present. She came because she wanted to conceive. If the routine of many clinics was followed she could not possibly conceive for the next 6 to 12 months. All special clinics should be stopped and a man seeing outpatients should, ideally, be prepared to carry out all the examinations and treatments he would do in private practice. He would comment on some of the methods adopted.

Cervical Dilatation

All sorts of different interferences with the cervix seemed to render a woman more likely to become pregnant; and this might be how insufflation or salpingography helped the patient. Perhaps the reaction of the cervix to mild infection or injury was to produce an easier flow of fluid mucus and that Nature intended this to take place by coitus. Perhaps this was why simple examination sometimes seemed to have removed the infertility. Perhaps this was all that happened when a retroverted uterus was corrected.

Rubin's test

He doubted very much whether there was any actual therapeutic value in the passage of gas through the tubes, any good result from insufflation or salpingography being more likely attributable to the irritation of the cervix. If adhesions could be broken down by blowing through the tubes, this would have no therapeutic value. The careful technique necessary in salpingostomy was well known. Deductions were made on the motility of the Fallopian tubes from the waves on the kymograph, but these waves were not due to tubal peristalsis.

Hormones

No hormone was known that would make a woman ovulate naturally, and he knew of no hormone treatment of infertility that was not just a mixture of hope and suggestion.

Tuberculosis

The discovery that completely symptomless tuberculosis could exist in the endometrium and that it was almost invariably associated with tubal tuberculosis had led to a lot of curetting and we were told that to be certain that tuberculosis was absent the complete endometrium had to be curetted out. Having discovered

tuberculosis we had to administer streptomycin up to 100 mg. with further curetting every 2 or 3 months.

He suggested that we had no idea of the natural history of symptomless and signless genital tuberculosis. If these women were left alone would they ever come to any harm? In time, and given good general health, the process would become quiescent and do no further harm —with an exception—as elsewhere in the body. If tuberculosis was mixed with simple sepsis or injury tissue destruction became very active. Symptomless genital tuberculosis might later produce symptoms and signs but it might be that the procedure necessary to make the diagnosis set off the activity of the disease. Secondly, streptomycin seemed to clear the miliary 2 or 3 weeks old, tiny tubercles in the endometrium quite well, but if reinfection occurred from the older, more developed, less vascular lesions in the tubes, even 100 mg. of streptomycin would be followed by further crops in the endometrium. Treated patients might cease to have endometrial tubercles but during treatment many months had elapsed and tuberculosis tended to cure itself with the passage of time. He would not be dogmatic and would not deny streptomycin to these patients, but we should be very critical of whether our examinations did harm and whether our antibiotic therapy did no good.

The Investigation of the Male Partner

Simple clinical investigation of the male might be revealing. Examination of the semen might show that he was infertile or deficient in one way or another, but the couple had not come to be told that he or she or both were of low fertility. They had come to be helped to have a child. In pursuing this line of enquiry a dreadful ogre had come into being—a seminologist. Around this so-called specialty the usual fantastic façade had been built. A man should not be pronounced deficient in fertility until at least 8 specimens had been examined. Dark hints were dropped in written articles that many seminologists were not really up to their job. The only qualifications a seminologist needed were that he could count and that he could recognize a normal spermatozoön when he saw one. If there were normal sperms present in any numbers the woman could become pregnant and that was what she wanted to know.

He knew of no treatment of any use in any form of male infertility. Testicular biopsy must never be done in the ordinary fertility clinic, for it was quite unnecessary that research should be repeated in every infertility clinic throughout the country. Unless there was some new line of enquiry, all the male partners should not be subjected to repeated examination to prove that they were infertile or relatively so—they had come to see if you could help them. As you could not treat sub-fertile men, you should leave them alone and tell them that pregnancy was possible. If there was azoöspermia, they should be told and left to face their disappointment.

His scheme for dealing with the infertile couple was:

1. Simple gynaecological examination of the woman.
2. Simple insufflation as an outpatient 4 or 5 days after menstruation had ceased. Whether the tubes appear patent or not, tell her that this may aid conception.
3. If conception had not taken place, carry out Huhner's post-coital test and if live sperms are seen in the cervical mucus do not trouble the male any further. If they are not, have a masturbation sample examined and only denounce him as the cause if no live healthy sperms are seen.
4. Take a specimen of the endometrium in the second half of the menstrual epoch with a Sharman's curette (this will not exclude tuberculosis but will show most cases).
5. Under an anaesthetic insufflate and dilate the cervix to a No. 10 Hegar 5 days after a period has ceased. If the tubes appear sealed carry out salpingography so that you can speak decisively.
6. Repeat the insufflation after a further 6 months and let that be the duration of treatment.
7. Throughout keep up an atmosphere of hope and encouragement.

Finally, said Mr. Stabler, it must be remembered that when a couple came complaining of sterility they were not complaining that they were ill—they were complaining merely of a dysfunction. To treat them as though they were ill or to make them ill by treatment was a grave disservice to them.

After Prof. A. M. Claye, Mr. T. Fitzgerald and Mr. W. Calvert had participated in the general discussion, Prof. Jeffcoate summed up. There had been a remarkable measure of agreement in principle. There was a general consent that measures of proved value must be differentiated from those still in the field of research. Most important of all in the management of infertility, due regard must be paid to the mental health of the couple concerned.

BOOK REVIEWS

"Human Embryology." By BRADLEY M. PATTEN. Second edition. Pp. xvii+798 with 453 illustrations. J. & A. Churchill, Ltd., London, 1953. Price 84*s*.

THIS is the second edition of Professor Patten's well-known book of Human Embryology (first published in 1946). It was designed to set forth in a simple and readable form the phases of human embryology which are of special interest to medical students. The careful selection of material and the rigid editing which the author used in the first edition have been retained in the present edition. This, however, has made it necessary to omit reference to comparative anatomy and to many theoretical considerations. In some respects this is to be regretted since there are many aspects of human development which cannot be appreciated if facts from comparative and experimental embryology are excluded.

Many parts of the present edition are unchanged except for minor additions and corrections. Two chapters, however, have been extensively rewritten, Chapter 4 which deals with Cleavage and The Germ Layer Formation and Chapter 6 on the Foetal Membranes and Placenta. Due to the outstanding contributions of Professors Hertig and Rock in securing earlier and earlier stages of human development these chapters are now based on human material. It is a pity that Professor Patten has not revised the section on the later stages of placental development. Much that has already been taken for granted is no longer considered to give an adequate description of the placenta.

We have no hesitation in recommending this book to the students who are about to embark on a subject which often appears to be more difficult than it should be.

W. J. Hamilton

"Mammalian Germ Cells." (Ciba Foundation Symposium.) Edited by DR. G. E. W. WOLSTENHOLME. Pp. xvi+302, with 54 illustrations. J. & A. Churchill, Ltd., London, 1953. Price 30*s*.

THE present volume contains the proceedings of a Symposium held under the title the "Physiology of the Mammalian Germ Cells" sponsored by the Ciba Foundation. Through the generosity of the Trustees of the Foundation it was possible for many scientists of international reputation to meet and discuss this subject.

A study of the many papers read shows that reproductive science has made very rapid progress during the past decade. A stage has now been reached when the applications of the many discoveries made may soon be expected.

The contents of this volume are divided into two parts. Part I deals with Spermatozoa and Part II with Ova. The germ cells are described and discussed not only from the morphological and physiological aspects but also from the biochemical. It is evident from the questions raised in the discussion following after each paper that many problems are still unsolved.

This book deserves the closest study by all individuals who are interested in reproductive physiology whether they are clinicians, veterinarians or research investigators.

Prof. Folley in his Foreword states that the advances reported in this volume are mainly applicable to stock-breeders, but, he goes on to say "The fact must be faced that they can also be applied to man, and society will have to consider seriously how best to handle these new possibilities which may be fraught with as much significance and danger of misapplication as the discovery of how to release the energy of the atomic nucleus".

W. J. Hamilton

"Carcinoma of the Female Genitalia." (The Abraham Flexner Lectures, Series 11.) By HANS LUDWIG KOTTMEIER, M.D. Pp. xii+213, with 59 illustrations. Williams and Wilkins, Baltimore, and Baillière, Tindall and Cox, London, 1953. Price 33*s*. 6*d*.

THIS book comprises a course of five lectures, given by Dr. Kottmeier, the Chief of the Gynaecological Section of the Radiumhemmet in Stockholm and the Abraham Flexner Lecturer for 1951 at the invitation of the Vanderbilt University Medical School.

The interesting introductory lecture on Sweden's Cancer Campaign Program is a historical survey of the development of radiotherapy in Sweden as well as an admirable description of the administration of the Radiumhemmet. The author then proceeds to discuss the development and classification of genital cancer in women with special reference to carcinoma *in situ*.

The last three lectures are entirely devoted to the discussion and evaluation of treatment, two being mainly concerned with radiotherapy of cervical and corporeal carcinoma, and the last dealing with the results obtained by surgery and critically comparing surgical and radiotherapeutic statistics.

An excellent review of the radiotherapeutical techniques in use as well as of the hazards of treatment is given. This is accompanied by numerous excellent radiographs, some of them stereoscopic, illustrating the application of radium according to the Stockholm technique. Dr. Kottmeier discusses the possibility of cure depending on 3 factors: (*a*) the delivery of a tumour control dose to the whole tumour bearing area, (*b*) the degree of malignancy of the neoplasm, and (*c*) the general condition of the patient.

The last lecture is devoted to comparing the results of surgical and irradiation treatment. Dr. Kottmeier's figures of 5-year apparent cure by radiotherapy compare very favourably with Dr. Meigs' 5-year cure rates after surgical treatment. It is not surprising that Dr. Kottmeier is a fervent adherent of radiotherapy and that he fights

eloquently against any claim that surgery may have advantages over radiotherapy. His views may be debatable and outside the Radiumhemmet he may stand alone. However, he states his case extremely well; some of his arguments are unusual and new and provide food for thought and further research.

This book, written by a man with great experience in the treatment of malignant disease of the female pelvis and coming from a school with the highest tradition, should take a place of honour in the library of every gynaecologist. *E. Wachtel*

"A Handbook on Cancer for Nurses and Health Visitors." By RONALD W. RAVEN. Pp. 104, with 21 illustrations. Butterworth & Co., Ltd., London, 1953. Price 12*s*. 6*d*.

THIS little handbook is divided into three sections: (1) Introduction, (2) the early diagnosis of cancer, and (3) the care of the patient with cancer.

The first part describes briefly cell-division in both normal and abnormal tissues, the definition of carcinomata, their varieties and behaviour and finally the theories of causation.

All this is done on five pages and, while credit is due to the author for his concise summing up of these elementary details, we feel that many of those to whom the book is addressed would have appreciated some expansion of these topics.

The second and major portion of the book deals in turn with the various organs of the body, describing first the pre-cancerous conditions encountered, early signs and symptoms, treatment and generalizations on prognosis. This section will tend to make the reader more "cancer conscious" and to bring the percentage of cancerophobes in this country more in line with the American figures.

The final section on nursing care gives simple instructions on cleaning colostomies, changing tracheotomy tubes, etc., and gives details of diets suitable for post-operative and convalescent patients.

This book is well written and well illustrated.

"Textbook of Gynaecology." By JOHN I. BREWER, B.S., M.D., Ph.D. First edition. Pp. xviii+532, with 146 illustrations. Baillière, Tindall & Cox, London, 1953. Price 76*s*. 6*d*.

THIS textbook, which emanates from the Northwestern University Medical School, Chicago, is in two parts. The first, without the customary introductory chapters on anatomy, embryology and physiology, describes the common gynaecological lesions systematically. Among these chapters, that on carcinoma of the cervix and particularly the section on carcinoma *in situ*, is outstanding as a model of precise and balanced writing. The second, larger, part of the book, without any preliminary chapters on the art of case-history taking and of routine examination, is devoted to the clinical approach. Symptoms and signs are dealt with as they would present clinically, and their investigation, differential diagnosis and treatment are then discussed, many chapters ending with a list of the possible causative lesions grouped for easy memorizing. It follows that many entities, fibroids for instance, appear for discussion in several chapters, but Professor Brewer, like most teachers, believes that repetition is good pedagogy.

Some statements in the text will raise gynaecological eyebrows on this side of the Atlantic; such as, that a sperm count of 60 millions or less per c.cm. represents a poor specimen; that pelvic tuberculosis can rarely be diagnosed before operation; that a papillary cystadenoma of the ovary is always clinically malignant. Nevertheless the teaching is basically sound and refreshingly conservative. In particular, the limitations of hormone therapy are reiterated, although large doses of oestrogens are recommended in endometriosis. The outstanding feature of the book is the excellence of the many photographs; these are so comprehensive that there are only two diagrams in the whole volume.

This textbook is avowedly for undergraduates and Dr. Brewer points out that in teaching them the principal aim is to prepare them to be good general practitioners, not specialists. This is agreed, but not everyone will approve when he goes on to say that the material taught should therefore be reduced to an amount that can be effectively taught and adequately retained by the student. Fortunately the book is not in fact quite so restricted, for such an attitude is likely to satisfy rather than stimulate, to produce a dogmatic rather than a balanced approach, and to lead the student to believe that gynaecology is more of an exact science and less of an art than it really is.

"Resuscitation of the Newborn." By JOSEPH D. RUSS, Assistant Professor in Pediatrics, Tulane University School of Medicine. Pp. vii+55, with 7 figs. Charles C. Thomas, Springfield, Illinois; Blackwell Scientific Publications, Oxford, 1953. Price 18*s*.

IN this monograph in the American Lecture Series the writer brings his experience of 2,000 resuscitations to a discussion of the classification, pathology and clinical causes of asphyxia in the newborn and to methods of resuscitation.

The methods of resuscitation advised follow commonly accepted procedures except that the virtue of tracheal aspiration is overstressed. The bibliography is extensive and includes many papers likely to be little known in Britain.

The discussion on classification and aetiology is confused and of little guide to the paediatrician or obstetrician. In view of the rapid strides in knowledge the author has not had an opportunity to include recent work which has done much to clarify problems of aetiology and treatment. *James Walker*

"Operative Gynecology." 2nd edition. By RICHARD W. TE LINDE. Pp. xxiv+902, 409 figs. Sir Isaac Pitman, London, 1953. Price £6 net.

THIS, the second Edition, follows the first edition after an interval of six years. It has some substantial additions including a section on Carcinoma *in situ*, which incor-

porates the important published contributions on this subject made by Professor Te Linde and his co-workers.

Despite its title the book does not restrict itself so exclusively to a description of the special operative procedures as does the British textbook, with which it invites comparison—Victor Bonney's *Textbook of Gynaecological Surgery*. Thus, out of a total of 902 pages no less than 108 are devoted to preoperative and postoperative care, the armamentarium, anaesthesia, opening and closing the abdomen, the use of pessaries and oestrogenic therapy of the menopause. There are 58 pages devoted to conditions of the anus, rectum, appendix and intestines. Moreover considerable space throughout is given to aetiology, pathology and symptomatology.

The teaching throughout is, on the whole, conservative and we have not found many occasions in which it differs fundamentally from that accepted by British gynaecologists. Dr. Te Linde's description of the factors responsible for uterine prolapse would not commend itself to all gynaecologists in this country and he regards the Manchester operation as unsuitable in cases of complete prolapse and in cases where subsequent pregnancy may be expected. He cites the experience of Fletcher Shaw in support of these claims. In his report of a follow-up of 549 women after the Manchester operation Shaw found that only 27 had children subsequently. This, Dr. Te Linde argues, indicates a high proportion of sterility or abortion. Moreover, Shaw found that 5 of the 27 women had recurrence of the prolapse, i.e., 18·5 per cent, which Dr. Te Linde regards as a further contra-indication. Dr. Te Linde prefers the Watkin's trans-position operation or the Spalding-Richardson operation for the routine treatment of prolapse. He speaks highly of the latter of which he records 400 without mortality and with a low recurrence rate. Described originally by Spalding in 1919 it remained unnoticed by gynaecologists until in 1937 Richardson published an account of a similar procedure which he had devised independently. The operation consists of amputation of the cervix, removal of the body of the uterus "at any level desired" through an anterior colpotomy opening, the use of the uterine portion and the broad and utero-sacral ligaments for interposition, and finally the approximation in the midline of the pubo-cervical fascia beneath the urethra, the base of the bladder and the retained part of the uterus.

A considerable section is devoted to an excellent discussion of the histology, diagnosis, prognosis and treatment of carcinoma *in situ* of the cervix. This section is illustrated with the most striking photomicrographs of this lesion which we have seen in any textbook. The standard treatment during the past 12 years has been a rather radical removal of the uterus and including an ample vaginal cuff.

This is a book of outstanding merit. It is invested with the authority of a well-known writer and of a great school of gynaecology. It is written in a pleasing, direct style and throughout the operative detail is illustrated lavishly with figures that are at once effective and artistic. The production in regard to paper, printing and binding is of a very high order. Altogether an achievement for author and publishers alike.

REVIEW OF CURRENT LITERATURE

CONTENTS

	REF.
ANATOMY AND PHYSIOLOGY	32
PREGNANCY	36
OPERATIONS	49
THE INFANT	50
GYNAECOLOGY	53

ANATOMY AND PHYSIOLOGY

32. **Study of the Supportive Structures of the Uterus by Levator Myography.**

By B. BERGLAS and I. C. RUBIN. *Surg. Gynec. Obstet.*, 97, 677-692. Dec. 1953. 26 figs. 16 refs.

The authors consider that investigation of the supporting structures of the uterus is important in the living female because postmortem loss of muscle tone alters the position of the muscular pelvic floor at the outlet, thus changing the relationship of the pelvic organs to the muscular pelvic diaphragm.

The levator ani muscles of both sides constitute a structural and functional entity which is composed of a plate filling the space between the coccyx and the anal portion of the rectum, and two crura forming the boundaries of the levator hiatus which is pierced by the urethra, vagina and rectum. The designation of levator plate and levator crura is adopted and proves helpful in the physiological study of the pelvic diaphragm.

To determine the relationship of the uterus to the levator ani muscle, study of the anatomy and the function of the muscle was undertaken in the living subject by the method of X-ray myography. A contrast medium was prepared containing half the usual amount of X-ray opaque substance contained in rayopake. This was found to be harmless to the tissues, practically painless during and after injection, and was eliminated by the kidneys within 2 hours.

With the patient in the lithotomy position 5 ml. was injected through the lateral vaginal walls into each levator crus. Ten ml. was then injected into the levator plate at a point in the midline midway between the tip of the coccyx and the posterior circumference of the anus. Seventy-three patients were investigated in this way.

Antero-posterior radiographs were taken with the patient positioned as for inlet pelvimetry and lateral radiographs with her in the standing position. The vagina and rectum were visualized by introducing small quantities of barium suspension and the uterus by the insertion of a metal stem pessary into its cavity.

The roentgenograms obtained in the living female with anatomically and functionally intact levator ani muscle show that at rest the levator plate has an almost horizontal course and that the uterus and vagina are situated over the plate and not over the levator hiatus. The cervix of the uterus lies upon the posterior part of the plate near its insertion into the coccygeal bone, and is separated from it by the posterior vaginal wall and the rectum. The vagina lies within the pelvis, almost parallel to the levator plate similar to the course of the terminal part of the rectum. When the rectum is filled, the uterus and vagina are forced forward, but the axis of the uterus remains poised over the plate.

It is shown that during a rise of intra-abdominal pressure, the visceral thrust from above in the pelvic cavity is directed backward and downward and pushes the uterus, vagina and rectum toward and against the levator plate, far behind the levator hiatus. Thus, with the pelvic diaphragm intact, the pelvic floor aperture is out of reach of the effect of intra-abdominal pressure on the uterus.

Anatomical or functional impairment of the levator crura changes the position of the levator plate within the pelvic outlet. Due to the weakened attachment of the levator ani muscle to the pubic bones, which under normal conditions is effected by the levator crura, the levator plate loses its normal resilience and tends increasingly to sag downward.

Increase in the inclination of the levator plate results in a corresponding increase of the longitudinal diameter of the pelvic hiatus and study of the levator myograms shows that there is a definite correlation between the inclination of the levator plate and the degree of uterine prolapse.

In the first degree prolapse of the uterus, the levator plate at rest has a horizontal course which favours the support of the uterus. However, on straining a considerable obliquity of the plate develops; this causes some degree of downward sliding of the uterus along the inclined plane of the levator plate, resulting in a dropping of the uterus.

In second degree prolapse of the uterus the levator plate shows while at rest a considerable inclination and the uterus is situated over the enlarged pelvic floor aperture. On straining with the loss of resistance to the intra-abdominal pressure, the levator plate assumes an almost vertical course giving little support to the uterus.

In third degree prolapse of the uterus, while the patient is erect and at rest, the levator plate has a vertical course, thus failing to give any possible support to the uterus. In such cases the force of gravity is sufficient to produce procidentia through the levator hiatus.

[The authors illustrate their deductions with many fine reproductions of radiographs and their careful study will well repay interested readers.] *John P. Erskine*

33. **Establishment of Endometrial Cycle after Delivery. Clinical and Histological Study.** (Restablecimiento del ciclo endometral después del parto. Estudio clínico e histológico.)

By R. SAMMARTINO, R. M. GORI and E. BAYONA. *Obstet. Ginec. Lat-amer.*, **11**, 1-10, 1953. 9 photomicrographs, 5 tables, 6 refs.

The histological pattern of the endometrium varies with the time of onset of menstruation after delivery. This investigation was made by taking endometrial biopsies from 104 patients on the first day of menstruation after delivery; in 40 per cent of these cases further biopsies were taken at subsequent menses.

The authors present their work in three sections: (1) a histological study of the endometrial material, which they classify under four sub-groups, (*a*) proliferative, (*b*) secretory, (*c*) hyperplasia, and (*d*) additional lesions.

(2) The grouping of the endometrial histology according to whether the menses had returned within 90 days of delivery, and whether the mother was lactating or not lactating.

(3) The same as (2) but in cases where menstruation had not returned within 90 days after delivery.

The authors found all stages of the proliferative and secretory changes that are normally found in the endometrial cycle. In the hyperplasia series, most cases showed simple hyperplasia; a few, however, showed carcinoma-like appearances. Under the heading of additional lesions, they described such findings as endometritis, remnants of chorion and areas of anomalous-looking epithelial cells. Most of the sections, however, showed different stages of endometrial histology.

In those lactating mothers whose menses began in less than 90 days after delivery, 57·4 per cent showed a proliferative endometrium, and 7·4 per cent a secretory endometrium, whilst, of the non-lactating cases, hyperplasia of the endometrium occurred most commonly in 40 per cent and secretory in 30 per cent. Where menstruation began more than 90 days after delivery, the endometrial findings were different: in the lactating mothers the secretory phase was found in 52 per cent and, in the non-lactating mothers, in 60 per cent. Thus is shown the influence of lactation on the ovarian cycle.

In biopsies taken at subsequent menses, it was found that the endometrial patterns were not always consistent with the previous ones. The time for the secretory phase to appear varied between 2½ months and 11 months.

The authors state that 75 per cent of the first menstrual biopsies showed oestrogenic stimulation only of the endometrium. *John F. Foulkes*

34. **The Stimulative Action of Chorionic Gonadotrophin on the Adrenal Cortex.**

By W. P. PLATE. *Nederl. Tijdschr. Verlosk.*, **52**, 384-393, 1953. 3 tables, 2 figs., 35 refs.

Professor W. P. Plate subscribes to Botella Llusia's view of the adrenal cortex as the "third gonad". His work purports to demonstrate that the secretion of gonadotrophins may stimulate the adrenal cortex to secrete oestrogens and androgens. From this point of view he considers the evidence available in the world literature regarding the effect of pituitary and chorionic gonadotrophins upon the adrenal cortex. An account is given of 3 patients, 2 castrate females and a male eunuchoid, to whom large doses of chorionic gonadotrophin were given. They were given Pregnyl in doses of 20,000 I.U. daily for 4 days. Oestrogens and vaginal smears were examined. All 3 patients showed evidence of increased oestrogen production and a rise in the level of urinary 17 ketosteroids. This is considered to be evidence of a gonadal function of the adrenal cortex, responsive to gonadotrophic stimulation. [The method of oestrogen assay is open to question although the photomicrographs of vaginal smears before and during treatment are convincing. Only one assay of pre-treatment levels was made in each case. The force of the argument is much weakened by the likelihood of ACTH being also present in the preparation used.] *A. Klopper*

35. **Vaginal Smears and Cytometry in the Diagnosis of Cyclical Patterns with Special Consideration of the Effects of Androgenic Substances.**

By W. LANGREDER and G. ZIMMERER. *Arch. Gynäk.*, **184**, 1-31, 1953. 10 illus., 2 tables, 84 refs.

The authors classify the exfoliated squamous cells in vaginal smears according to the cell type (superficial squames divided further into 3 subgroups, intermediate squames and basal cells), the cell size, the nuclear size, the glycogen content and the cell turgescence. Characteristic patterns during the different phases of the cycle and after the menopause are described. Administration of testosterone in postmenopausal women is shown to have a stimulating effect on the epithelium if given in small doses. Testosterone was given in the form of vaginal pessaries in doses of 1·2 mg. methyltestosterone.

Cytometric comparison of smears in normal untreated women with those receiving methyltestosterone suggests to the authors the presence of a "physiological androgenic phase" during the early proliferative phase of the cycle. This androgenic influence appears to reach a peak value on the 5th day of the cycle and can be abolished by oestrogen administration. The authors conclude that the epithelial patterns obtained in the proliferative phase are the effects of the alternating action of 2 hormones. They suggest that the cause for the postmenstrual increase in

libido is to be found in the presence of the cytologically recognizable androgenic substances.

The interaction of androgenic, oestrogenic and luteinizing hormones can be recognized in smear patterns. There is, as a rule, no abrupt cessation of hormonal activity after the menopause. Atrophic patterns soon after the cessation of menstrual periods are an exception. Usual findings are "persistent hormonal effects" with either oestrogenic, androgenic or luteinizing predominance. Persistent androgen effects were found in 1 in 10, persistent progesterone effects in about 3 in 5 of all postmenopausal women examined. No figures for persistent oestrogen effects are given. "Mixed patterns" were found frequently. *E. Wachtel*

PREGNANCY

36. Physiological Properties of Amniotic Fluid during Pregnancy and at Parturition.

By O. STAMM. *Gynaecologia, Basle*, **136**, 377. Dec. 1953. 9 figs., 38 refs.

Amniotic fluid has been recovered from the uterus during normal pregnancy between the 15th and the 25th week of gestation and during normal labour at term. The fluids thus obtained were tested on the guinea pig uterus in vitro.

Amniotic fluid collected during labour (amniotic fluid of delivery or AFD) in 50 cases was tested in 50 different guinea pig uteri. It was found that either tetanic contraction occurred or spontaneous activity was considerably increased. Thus an oxytocic effect was demonstrated but this was not due to posterior pituitary hormone since it was not destroyed by boiling with alkali. It did not appear to be due to histamine or acetylcholine. Amniotic fluid of pregnancy (AFP) showed no oxytocic activity and indeed had a muscle relaxing effect.

It is concluded that during labour the amniotic fluid contains a powerful oxytocic factor which is not posterior pituitary hormone and is not histamine or acetylcholine. *Josephine Barnes*

37. Artificial Hypothermia (so-called "Artificial Hibernation") in Obstetrics and Gynaecology. (Presupposti teorici e ricerche sperimentale e cliniche sulla ipotermia artificiale nel settore ostetrico e ginecologico.)

By G. VALLE, *et al. Minerva ginec.*, **5**, 549-569, 1953. 12 figs. 87 refs.

The authors point out that the normal reaction to cold by increased metabolism can be an unnecessary strain on the resources of an individual already weak from illness; so much so that only by blocking the normal heat-regulating mechanism can one obtain the benefit of an immediate slowing down of all biological activity. By using the accepted physical and pharmacological measures, the authors obtained a fall of temperature up to as much as 18° F. (i.e., to 28° C.) in certain cases of hyperemesis, eclampsia, of normal and operative delivery, and in certain prolonged operative procedures.

The method was adjudged to be very useful in "incoercible" cases of hyperemesis and useful in eclampsia, also useful in prolonged operations in which a "silent" abdomen was obtained with much reduced amounts of anaesthetic. Artificial hibernation was also found useful for immature infants where remarkably low temperatures (29° and 30° C.) were maintained for 8 to 12 days on end.

However, the authors admit that this hibernation technique has its disadvantages—in labour uterine inertia with foetal bradycardia may occur [the latter one would think an advantage] and foetal apnoea and drowsiness were apt to cause concern after delivery. Moreover, a specialized and instructed type of supervision is needed, the normal response to low temperatures being to rush forward with hot water bottles [From my acquaintance with the devoted but obstinate religious orders who provide so much of the nursing in Italy, I can well believe this point.]

Whilst considering that the technique has no place in ordinary obstetric and gynaecological procedures in healthy patients, the authors recommend its trial in severe cases of hyperemesis, and for severe operations and grave infections in debilitated persons. *W. C. Spackman*

38. Effects of Apresoline, Veratrum Alkaloids, High Spinal Anesthesia and Arfonad on Renal Hemodynamics of Pregnant Patients with Toxemia and Essential Hypertension.

By S. A. KAPLAN and N. S. ASSALI. *Surg., Gynec. Obstet.*, **97**, 501-507, Oct. 1953. 9 figs. 9 refs.

Reduction in renal blood flow and glomerular filtration rate associated with increased renal vascular resistance is usually present in toxaemia and essential hypertension.

The authors assume on theoretical grounds that further increase in renal vascular tone would be an undesirable side effect of a vasodepressor agent used in the management of hypertensive states complicating pregnancy.

With this in mind they investigated the effects of some of the newer vasodepressor agents on renal haemodynamics. Apresoline (1-hydrazinophthalazine), several veratrum preparations, high spinal anaesthesia with procaine solution and arfonad (RO2-2223) were selected. Studies were performed on 17 patients with toxaemia of pregnancy, 7 with essential hypertension and 6 with normotensive pregnancy.

It has recently been demonstrated that apresoline has the unusual property among vasodepressors of producing vasodilatation of the renal vessels in non-pregnant subjects. The authors were able to show that in pregnant patients with toxaemia or essential hypertension the drug both lowered the blood pressure and reduced renal vascular resistance.

The veratrum alkaloids tended to increase renal vascular resistance, but since observations were not extended beyond 1 hour after drug administration, information is not available on whether relaxation of renal vascular tone ultimately occurs.

Both arfonad and spinal anaesthesia were found to produce increased renal vascular tone whenever a hypotensive response was induced.

The authors conclude that on the basis of its power to

lower the blood pressure and to relax renal vascular tone in pregnant patients with toxaemia or essential hypertension apresoline appears to be an important addition to the armamentarium of drugs for the therapy of these two complications of pregnancy. *John P. Erskine*

39. Postabortal Sepsis due to Clostridium welchii. By G. W. Douglas, B. H. Carney and D. Pellillo. *Surg., Gynec. Obstet.*, **97**, 490-500. Oct. 1953. 7 figs., 30 refs.

This report deals with 6 cases of postabortal sepsis due to *Clostridium welchii*, in which the fulminating form of the disease and the later problem of oliguria are well illustrated.

The finding of haemoglobinuria, haemoglobinaemia, jaundice and rapidly progressive anaemia in a postabortal patient who appears more seriously ill than the temperature would ordinarily indicate should call the clinician's attention to the probability of *Clostridium* infection. The diagnosis can be confirmed at once by the finding of the organism in large numbers in smears from the cervical canal or interior of the uterus. The condition may be confused with acute yellow atrophy of the liver, ingestion of toxic abortifacients and with other septic conditions associated with abortion.

In the treatment, penicillin appears to be the drug of choice, and it has the advantage that enormous blood levels can be tolerated easily (as may occur during oliguria). The newer antibiotics may be effective but their use and safety in this condition have not been fully investigated.

The authors stress the similarity of oliguria complicating postabortal sepsis due to *Cl. welchii* and lower nephron nephrosis due to other causes. They suggest that many of the reported cases of oliguria complicating septic abortion may have been due to *Cl. welchii* septicaemia. This is suggested because, in their experience, vaginal smears may be inconclusive unless taken before antibiotic therapy is begun, and septicaemia of pronounced degree may exist despite negative blood cultures. *Cl. welchii* requires rigid anaerobic conditions for its successful growth in culture, and failure to provide these conditions is a frequent source of error.

If postabortal oliguria is generally related to *Cl. welchii* septicaemia, one puzzling aspect of the condition, its rarity, is neatly explained. The low frequency of postabortal oliguria parallels that of postabortal sepsis due to *Cl. welchii* and it is noteworthy that this is the only organism encountered in postabortal sepsis which frequently produces a potent haemolysing toxin.

John P. Erskine

40. Painful Hydatidiform Mole. (Mola distopica terebrante.)

By Fermin R. Merchante. *Obstet. Ginec. Lat-amer.*, **11**, 451-455, Oct. 1953. 2 photomicrographs.

A case of a perforating type of hydatidiform mole is reported in a patient aged 24 years. At 8-weeks gestation vaginal bleeding was thought to be due to a threatened abortion and, when it recurred and persisted, curettage was performed, but no evidence of pregnancy was found. Amenorrhoea continued, however, and lower abdominal pain developed. In the 8th month from the cessation of normal menstruation the patient was admitted to hospital as a surgical emergency. Pain was present over the whole abdomen and especially in the right lower quadrant, where a mass could be felt. This on vaginal examination was estimated to correspond to the size of an 8-months foetal head; its consistency was described as hard on the medial aspect, and soft laterally. Blood examinations were normal, and a Manini pregnancy diagnosis test was negative.

Two days later, because the pain was getting worse, a laparotomy was performed. A mass, the size of a grapefruit, was found in the right broad ligament, to which colon and ileum were adherent, and an erosion was present on the posterior aspect of the uterus, from which blood was oozing into the peritoneal cavity. Incision of the mass revealed a degenerated hydatidiform mole, and an offensive odour suggested that a *Bact. coli* infection was also present.

Sub-total hysterectomy and removal of the mole were performed. Examination of the specimen revealed that the pregnancy had implanted itself in the interstitial part of the Fallopian tube, and the hydatidiform mole that had developed had not only penetrated posteriorly into the peritoneal cavity, but had also spread extensively into the parametrium. *John F. Foulkes*

41. Vaginal Atresia and Pregnancy. (Atrésie vaginale et grossesse.)

By A. Hollaender and L. Lindemans. *Gynéc. et Obstét.*, **52**, 386-390, 1953.

For a long time vaginal atresia was considered largely of congenital origin, due to embryological malformation of the foetus, or to previous infection involving the child's genitalia.

Neugebauer's observations are quoted; this author described 720 cases, in which the cause was determined in 465—that is to say in two-thirds of the cases the precise cause was known. He concluded that congenital atresia of the vagina was rare and usually was associated with either a rudimentary uterus or complete absence of the uterus.

Acquired atresias present quite a different aetiology depending on the date of their appearance in the course of the life of the woman.

The writers agree with King (1922) as regards the classification of atresia into that occurring (1) during infancy, (2) after the menopause, and (3) during the sexual life of the woman.

(1) *During Infancy*—injuries and vaginal infections due to streptococci, diphtheria, and above all to gonococci are the most common causes. The role of exanthemata is open to discussion.

(2) After the menopause the cause is atrophic vaginitis with superadded infection. On examination the vaginal vault is retracted into a cone shape and the cervix is not always visible. If a too vigorous vaginal examination is made by artificially breaking certain adhesions, bleeding may occur, making the observer suspect malignant degeneration. However, examination with the speculum shows that it is the freed areas that exude drops of blood

and the appearances are different from those of cancer of the cervix.

(3) During the fertile life of the patient acquired stenosis can form sometimes an insurmountable obstruction to birth. At the Strasbourg gynaecological clinic where the writers work there were only 2 cases between 1946 and 1952—that is 0·018 per cent. In one there was a history of trauma during instrumental delivery. In the other there was gonorrhoea and pyocolpos.

In 25 cases of acquired atresia in the literature of the last 50 years, they found the following causes in order of frequency:

(1) Injection of caustic substances—13 cases.
(2) Birth trauma—6 cases.
(3) Vaginal stenosis in elderly primigravida—2 cases.
(4) Coital injuries—2 cases.
(5) Diphtheria in infancy—1 case.
(6) Post-operative stenosis—1 case.

D. Maxwell

42. Diabetes and Pregnancy.

By E. Tolsti, W. P. Given and R. G. Douglas. *J. Amer. med. Ass.*, **153**, 998-1002, 14th Nov., 1953. 6 refs.

These authors have previously published the results of 131 diabetic pregnancies in which the viable foetal mortality was 24·8 per cent (*Amer. J. Obstet. Gynec.*, **59**, 729-747, 1950). Following this they established a group of specialists in various fields to control diabetic pregnancies and the present paper records their results with 72 cases treated by this group at the Women's Clinic of the New York Hospital. The foetal loss in this group has been reduced to 22·2 per cent with no maternal death. They did not perform any therapeutic abortion in this series, but had they done so it would have reduced their loss of viable foetuses still further.

No hormone therapy was used in their treatment which is based on clinical methods and weekly examinations. All patients were given 6-8 g. of ammonium chloride daily for 4 days of each week and salt was restricted as far as possible. Unweighed, self selected diet was permitted, with enough insulin to avoid ketosis. All patients were admitted to hospital at the 35th week for evaluation. The complications they regard as most serious are hydramnios, ketosis, and toxaemia. The appearance of any of these after the 34th week is an indication for delivery, usually by Caesarean section under local anaesthesia. A paediatrician assumes complete charge of the infant at birth and the neonatal routine includes regular stomach aspiration, antibiotics for 10 days, and digitalization if there is cardiac enlargement on screening or if the liver is grossly enlarged. All the infants lost were from mothers showing one or more of the complications referred to above. Every effort is made to avoid ketosis, but this usually responds to vigorous treatment in hospital. There is no specific treatment for hydramnios or toxaemia at present. They favour premature delivery but emphasize the difficulty in deciding the exact time.

There is great difficulty in classifying the severity of diabetes, but the authors conclude that favourable results can be obtained in the pregnant diabetic without the use of hormones and by employing clinical methods for treating the diabetes.

D. W. James

43. Rheumatic Heart Disease complicating Pregnancy.

By M. I. Drury, M. K. O'Driscoll, T. D. Hanratty and A. P. Barry. *Brit. med. J.*, **1**, 70-73, 9th Jan., 1954. 9 refs.

Improvements in maternal mortality rates from strictly obstetrical conditions have in the last 50 years been so great that rheumatic heart disease becomes relatively more important and in the last decade has rivalled haemorrhage, eclampsia and sepsis as a serious complication of pregnancy. To evaluate the problem, the authors studied 250 pregnancies in 175 women during a 4-year period starting in 1948. The average parity of these women was 4 and they had had a pregnancy on an average every 2 years. No therapeutic abortions had been performed, for the series was drawn from a population which did not practice prevention or termination of pregnancy. By the end of the survey, 11 women had died, 6 of them during pregnancy or in the following year (3·5 per cent maternal mortality) and the others later than that, so that their deaths were not considered to have been related to pregnancy. The uncorrected foetal loss was 6·4 per cent.

An unequivocal rheumatic history was given by 63 per cent of the cases, the vast majority having mitral stenosis. Confirmation was obtained in this series for the view that the heart deteriorates with increasing parity, but the analysis on age shows that in general the severity can similarly be related to increasing years. A striking exception to this was the large number of severe cases under 26 years old and it appeared that recurrences of acute rheumatism might explain this anomaly.

Cardiac failure was diagnosed in 29 cases and auricular fibrillation, acute infections, anaemia, hypertension, fluid imbalance, active rheumatism and bacterial endocarditis seemed to be the precipitating causes of the breakdown. The failure occurred by the 28th week in 9 of them, and in 14 between the 28th and 36th weeks. Five broke down in labour and 1 during the puerperium.

Labour was induced only for reasons other than the cardiac condition and the same applied also to the use of Caesarean section except for 1 case in the early days of the survey. The abdominal delivery rate was 3 per cent, and 6 women were delivered vaginally after previous section for heart disease. Timely, but not routine assistance with vaginal delivery is advocated, using local analgesia supplemented if necessary with intravenous thiopentone, and the assisted vaginal delivery rate of 20 per cent was twice that for all the hospital deliveries.

There were no maternal deaths amongst the booked cases but 6 (20 per cent) of the unbooked ones died after admission in failure. Two were young primigravidae who died of congestive failure at 16 and 30 weeks, respectively, before delivery. Two other young primigravidae also succumbed to congestive failure, one 6 weeks after delivery with active rheumatic carditis and the other 10 weeks post-partum with subacute bacterial endocarditis. A gravida-2, aged 27, survived by only 5 hours a rapid delivery at 32 weeks of a stillborn foetus. Her failure had been precipitated by pneumonia. The only fatal case in the higher age or parity groups was a gravida-10, aged 39, who ruptured a previous classical

Caesarean scar in pregnancy. The 5 women who died more than a year after delivery were aged 33-48 years and all died from heart failure.

The stillbirth and neonatal death-rate in the series was comparable with that of the hospital's overall figures and study not only of the pregnancies observed, but of the past histories of these women, showed a low rate of abortion. The foetal loss was directly related to the heart disease in the 2 cases who died undelivered and may have contributed to 2 stillbirths associated with congestive failure. The authors state that the prospects of a healthy child are virtually the same as for a mother who has no heart disease.

Their conclusions are that there is no place for therapeutic abortion, sterilization, induction of labour or Caesarean section in the management of women with cardiac disease. Early diagnosis is all important, so that systematic rest and hospitalization, when necessary, can be advised. The standard treatments for decompensation, if it arises, are adopted and valvotomy is now an additional weapon. Vaginal delivery should be assisted if the second stage would otherwise not be short. Post-partum haemorrhage should be controlled, venesection being a much safer method of reducing blood volume when necessary.

Doreen Daley

44. Tuberculous Meningitis during Pregnancy and the Puerperium since the Advent of Streptomycin. (Méningites tuberculeuses au cours de la puerpéralité depuis la streptomycine.)

By M. Leroux and E. Guillet. *Gynéc. et Obstét.*, **52**, 391-398, 1953. 21 refs.

In 1948, 1949 and 1950 the opportunity was offered to the writers—a rare thing at that time—of observing the therapeutic effect of streptomycin on the syndrome of tubercular meningitis. In the course of the study, previous pathological conceptions concerning tuberculous meningitis had to be modified.

(1) Tuberculous meningitis may remain latent for a considerable time or only expresses itself in laboratory findings particularly the result of the cerebro-spinal fluid examination.

(2) It is often associated with acute miliary tuberculosis and cannot be diagnosed at this stage, except by repeated lumbar puncture.

The 7 cases published are not only of interest in themselves but certain of them demonstrate the remote effects of streptomycin.

Of the 7 cases described the average age was 25. Two were para-1, three were para-2, and two were para-4. One only gave a previous history of tuberculosis. Three succumbed to miliary tuberculosis and meningitis. Two died in the course of treatment, 1 was cured of meningitis and was well on the way to cure of the pulmonary tuberculosis. Three showed localized meningitis—1 died rapidly prior to any treatment and 2 others might have been considered cured. In all 4 died; 3 were cured.

The onset occurred in 4 in the second trimester, in 1 in the third trimester and in 2 following confinement. Labour started spontaneously before term between 6 and 8½ months in 4 cases, at term in 1, and there was 1 post-mortem Caesarean section 45 minutes after death. As regards the infants, all were born alive, including the case of postmortem Caesarean section performed 45 minutes following apparent death. One infant survived only 2 hours. One survived for 15 days and showed congenital tuberculosis. One died 12 days after delivery from miliary tuberculosis and tuberculous meningitis. One succumbed at 10 weeks. One was in excellent health 6 months later. One infant born on 14th February, 1949 was alive and well at the time the paper was written. The remaining infant born on 9th June, 1949 was alive and well at the time the paper was written.

These findings lead us to modify our views on meningitis associated with or without miliary tuberculosis. Prior to the introduction of streptomycin, the outcome of this type of case was always death. Since the advent of antibiotics, however, the results have been progressively improved, depending on early diagnosis and systematic treatment.

Early diagnosis of tuberculous meningitis uncomplicated by pregnancy is difficult enough—and certain symptoms are common to both pregnancy and meningitis. At the onset vomiting due to functional and nervous causes must be eliminated. Cerebral oedema with retinal changes caused by a cerebral tumour, true epilepsy, epidemic encephalitis, tetany and chorea all require to be considered.

In the puerperium, diagnosis is still more difficult. Post-partum infection may increase the delay in diagnosis; cerebral thrombophlebitis in particular may simulate meningitis.

In all their successful cases treatment had been very early. In their 3 cured cases the development of meningitis had scarcely been modified by the pregnancy.

The treatment is the same as that when the patient is not pregnant and it necessitates admission to hospital. To this can be added a course of calcium and vitamins as in all cases of pregnancy. Frequent clinical examinations are vital, and there should be monthly X-rays of the lungs and retinal examinations at frequent intervals.

From the obstetric point of view the authors agree that (1) therapeutic abortion is not advised; (2) if possible wait to term or viability and only intervene during the period of viability if the diagnosis is made too late, or a brief fatal issue is foreseen. This is the only indication for prophylactic Caesarean section; (3) oxygen therapy should be given during labour and penicillin in the days following delivery to prevent superadded infection; (4) finally histological examination of the placenta should be performed with culture of cord blood and also guinea pig injection of cord blood. The child must be isolated.

D. Maxwell

45. Adenocarcinoma of the Corpus Uteri and Pelvic Tuberculosis Complicating Pregnancy.

By J. A. Wall and J. A. Lucci. *Obstet. Gynec.*, **2**, 629-635, Dec. 1953. 8 figs., 16 refs.

From Texas comes the report of a case of endometrial cancer and pelvic tuberculosis complicating the same pregnancy. The patient, a gravida-3, had a cervical biopsy performed when she was 6-months pregnant

because of post-coital bleeding. This showed an adenocarcinoma. At 7-months gestation, a classical Caesarean section was performed, and a live child born, which died 5 days later. Six weeks post-partum the patient was given radium therapy; at this time curettage showed endometrial cancer, and cervical biopsy the same picture as before. Following this there was pyrexia with the development of an inflammatory pelvic mass. Six months after the radium treatment, total hysterectomy and bilateral salpingo-oöphorectomy was done. There were dense pelvic adhesions and evidence of perforation at the fundus of the uterus. Post-operative treatment included deep X-ray therapy. Histological examination confirmed carcinoma and also revealed caseous tuberculosis in the myometrium. The patient was given streptomycin and P.A.S. therapy. She made good progress.

J. G. Dumoulin

46. Recent Childbirth and Pulmonary Tuberculosis.

By D. T. O'Driscoll. *J. Irish med. Ass.*, **33**, 172, Nov. 1953.

In view of the large number of women admitted within one year of the birth of the last child to a sanatorium to which the author was attached, it was decided to investigate the possibility of an association between recent childbirth and pulmonary tuberculosis. Data were collected from eight sanatoria. In each sanatorium the total number of female in-patients between the ages of 15 and 45 years on 1st June, 1953 was ascertained; the percentage of these women who had contracted tuberculosis within 1 year of childbirth was calculated. Those patients who had suffered from tuberculosis before the birth of the child or those in whom the disease appeared after abortion were excluded from the investigation. The estimated percentage of women in the state who were within 1 year of childbirth was provided by the Central Statistics Office. Apart from the 35 to 39 age-group the investigation produced no evidence that women within 1 year of childbirth are more liable to develop pulmonary tuberculosis. The author offers no explanation for the apparent association between the disease and recent childbirth in the age group 35 to 39 years. In this investigation the author found no evidence to support the claim that, the later in pregnancy the diagnosis of tuberculosis is made, the worse the prognosis.

Dr. O'Driscoll emphasizes that despite these findings it is most important that the problem of tuberculosis in the pregnant patient should ever be kept in mind and that the necessity for suitable accommodation for active cases and their newborn babies is urgent. *J. K. Russell*

47. Diagnosis of Tubal Pregnancy by the "Graduated Frog Test". (Diagnosestellung der Tubargravidität durch den "Abgestuften Froschtest".)

By W. Lammlein and H. Lewin. *Gynaecologia, Basle*, **136**, 332, Dec. 1953. 41 refs.

Attention is drawn to the value of pregnancy tests using various amphibians for the diagnosis of abnormalities of early pregnancy with special reference to tubal pregnancy. The method used is that of Hartleb (*Geburtsh. Frauenh.*, **10**, 938, 1951). Frogs or toads are employed and are injected with concentrated urine and with urine in various dilutions. The reaction is described in 7 grades, the first being with urine concentrated 10 times and the seventh with urine diluted 100 times.

Its value is illustrated in certain cases. In one, a diagnosis of tubal pregnancy was made on the persistence of a positive reaction, while in another case operation was avoided because the test was persistently negative.

Josephine Barnes

48. Results of Conservative Operations in Tubal Pregnancy. (Zur Berechtigung der konservativen Operation bei der Tubargravidität.)

By B. Szendi. *Gynaecologia, Basle*, **136**, 327, Dec. 1953. 5 refs.

The author has performed 15 conservative operations for tubal pregnancy during the past 10 years. In 2 of these full-time pregnancy occurred while in a third the tubal pregnancy recurred.

He recommends evacuation and conservation of the affected tube at operations for tubal pregnancy, if the opposite tube is missing and if the woman has no living children. *Josephine Barnes*

OPERATIONS

49. Caesarean Section.

By E. Fletcher and F. A. MacDonald. *Obstet. Gynec.*, **2**, 593-602, Dec. 1953. 14 refs.

The authors review 567 Caesarean sections in the New York Lying-in Hospital for the years 1950-1952 in an attempt to assess the changing trends in the use of this operation. Its incidence was 4·2 per cent of all deliveries in 1951 and 5·1 per cent in 1952 compared with an average of 3·7 per cent for the years 1932 to 1952. In recent years there had been fewer sections for contracted pelvis, which was considered to be partly due to a real decrease in the incidence of this condition. In 150 operations (26·5 per cent) the indication was a previous Caesarean section in spite of an increased incidence of vaginal deliveries after previous Caesarean section. Two-thirds of all cases of placenta praevia were sectioned compared with 27 per cent of all cases of premature separation of the placenta. Two-thirds of 66 cases of diabetes in pregnancy were terminated by operation, which was used more frequently also in the elderly nulliparous patient. Cardiac disease and tuberculosis were no longer indications for Caesarean section, nor was prolonged labour, although 8 sections were done for "lack of progress". The most frequently used type of anaesthesia was local infiltration combined with inhalation or pentothal. As a general routine the transverse lower segment operation was performed although the classical operation was done in 20 per cent of cases. The gross infant death rate was 5·3 per cent, and details are given of the various groups contributing to this figure. The broadening of indications for Caesarean section to include foetal distress and maternal diabetes, whilst saving life, produces an increase in the infant death rate from section. For example, in foetal distress, including prolapse of the cord, the corrected infant death rate was 9·8 per cent. *J. G. Dumoulin*

THE INFANT

50. Bacteriology of Air and Dust in a Maternity Hospital.

By F. MARSH and H. E. RODWAY. *Lancet*, **1**, 125-127, 16th Jan., 1954. 7 tables.

The authors record their investigations into the bacteriology of the air and dust in the lying-in wards of a hospital where the babies are nursed in cots beside their mothers' beds. The bacterial colonies isolated consisted chiefly of sarcinae, *Micrococcus pharyngeus*, *Staphylococcus albus*, a coliform bacillus and *Bacillus subtilis*. Occasional colonies of *Staphylococcus pyogenes*, a pneumococcus and a non-haemolytic streptococcus were observed and on 2 occasions a few colonies of haemolytic streptococcus were seen. The bacterial counts were made from plates exposed for an hour over different periods during 24 hours. The first part of the experiment was carried out in two 4-bed lying-in wards and showed that the average count of bacterial colonies was maximal between 5 a.m. and 5 p.m. when activity in the ward was greatest. Separate plate counts showed a rise during ward activity, especially during bed-making. The second part of the investigation was carried out in single wards of a segregation block where the results of disinfection of blankets and bedding were tested. The authors found that the covering of blankets with cotton wrap made no difference to the colony counts, that spraying the air and blankets during bed-making was not an effective means of preventing or reducing the scattering of bacteria, but that disinfection of blankets, mattresses and pillows produces a fall in the bacterial counts. The third part of the investigation consisted of routine disinfection of blankets and sterilization of mattresses and pillows after use from November 1952 to July 1953. Bacterial colony counts made from time to time showed the lowest counts obtained at any time in the experiment. Although the bacterial colony counts were very low and colonies of *Staph. pyogenes* were not commonly seen, this was not correlated with a low infant nasal carrier-rate for *Staph. pyogenes* during the second week of life. The organism was found in 237 of 281 swabs taken from the 8th to 10th day of life. The total number of cases in which the organism was present in the baby's nasal swab and in the mother's nasal, breast or hand swab was 78 out of 123 cases. The presence of the organism in the nostrils of newborn babies did not seem to harm them.

H. H. Fouracre Barns

51. Emergencies in the Newborn.

By G. COOPER, M. BIRDSONG and R. BRADSHAW. *J. Amer. med. Ass.*, **152**, 1077-1080, 21st Nov., 1953. 5 figs., 10 refs.

In spite of a very high percentage of hospital deliveries neonatal mortality rate for the first few days of life has not declined as rapidly as it has for the period between the 2nd and the 12th month. The authors discuss the early diagnosis of respiratory embarrassment, abdominal masses, and atresia at various levels of the alimentary tract from the oesophagus to the anus. Abnormal respiration or cyanosis calls for immediate radiological examination unless the child is too delicate to be disturbed. This may lead to the discovery that atelectasis is secondary to bronchial obstruction which indicates bronchoscopy and suction. Pulmonary aplasia, hyaline membrane syndrome, pneumothorax and cystic disease are occasionally found, and of these the last two can be treated surgically. Diaphragmatic hernia may cause sudden death and early surgical repair is advocated.

Abdominal masses other than liver and spleen are most often due to polycystic kidneys or hydronephrosis if cystic, and to a neuroblastoma or Wilms's tumour if solid. Radiology, including pyelograms, is helpful in deciding whether surgical treatment is possible. Brief reference is made to 4 cases of successful thoracotomy with lobe resection for pulmonary cystic disease in infants under 4 weeks old.

Radiological examination of the alimentary tract should always be made in cases of suspected obstruction before surgical treatment. When a contrast medium is necessary iodized oil rather than barium emulsion is preferred for this purpose owing to the danger of aspiration.

[This paper was originally read before the joint session of the paediatric and radiological section of the American Medical Association. The title is a little misleading in that it is chiefly concerned with radiological diagnosis in the newborn, but in this respect it contains a great deal of useful information.] *D. W. James*

52. Congenital Absence of Both Kidneys.

By P. E. SYLVESTER and D. R. HUGHES. *Brit. med. J.*, **1**, 77-79, 9th Jan., 1954. 3 tables, 14 refs.

Agenesis of both kidneys is rare, only 171 cases having been reported before the present 4 cases which occurred amongst 9,940 deliveries at the West Middlesex Hospital. Other congenital abnormalities are usually present and the sex incidence is predominantly male. Bilateral agenesis is compatible with intrauterine life and does not seem to affect the quantity of liquor amnii. Survival after birth is short but 1 recorded case lived 21 days.

One case is described in detail, the infant being delivered by Caesarean section for placenta praevia. He had a lax skin and showed hypotonia and cyanosis. The skull was scaphoid and the anterior fontanelle tense. Death occurred with respiratory failure 20 hours after delivery. The only obvious congenital abnormality was a deformed pinna but postmortem revealed complete absence of both kidneys and ureters. Summary of the features of 3 other cases occurring at the hospital showed a tendency to abnormal skull shape, cyanosis and other congenital lesions not associated with the urinary tract.

An interesting suggestion is made that the lesion in the case described was associated with attempts to procure abortion 6 weeks after the last menstrual period. The mother had taken at least 2·3 g. of a quinine salt within 24 hours and later 85 ml. of an ergot mixture. The critical period of renal formation is between the fourth and sixth weeks of intrauterine life and in a 6-weeks embryo the external ear is starting to develop.

Doreen Daley

GYNAECOLOGY

53. Latent Female Genital Tuberculosis. Further Studies on its Diagnosis, Prognosis and Treatment. A Report on 100 Cases.

By I. HALBRECHT. *Gynaecologia, Basle*, **136**, 321, Dec. 1953. 7 refs.

In a series of 2,000 sterile women, 100, or 5 per cent, were found to be suffering from latent genital tuberculosis. All but 2 of the patients with tuberculosis were immigrants to Israel from Eastern Europe, the Balkans, North Africa and the Middle East, all regions where tuberculosis is prevalent.

Diagnosis was made on endometrial biopsy or on culture of menstrual discharge or on a combination of both methods. In two cases positive cultures were obtained from intermenstrual cervical discharge and in these culture of menstrual fluid had been repeatedly negative. The author recommends culture of both menstrual and intermenstrual discharges.

Of the 100 cases originally diagnosed, 46 have remained under observation for periods of up to 10 years. In all but 4 of these the tuberculosis remained clinically latent. The 4 cases developed pelvic peritonitis after salpingography, endometrial biopsy or local radium application. Two other women died, 1 of pulmonary and 1 of generalized tuberculosis. In 4 cases spontaneous cure appeared to occur. No case of pregnancy was seen.

Streptomycin in a total dose of 45 grammes was given to 20 patients and in 14 of these bacteriological cure was obtained. Four of the remaining 6 cases became negative after treatment with a further course of streptomycin and P.A.S., 10 to 14 grammes daily. The remaining 2 cases remained positive in spite of two courses of treatment.

It is concluded that treatment with streptomycin is the most promising line of attack in female genital tuberculosis. *Josephine Barnes*

54. On the Variable Meaning of Amenorrhoea. Suggestions for Diagnosis and Therapy. (Sul diverso significato dell'amenorrea. Proposte per la diagnosi e la terapia.)

By E. PHILIPP. *Riv. Ostet. Ginec.*, **8**, 213-221, Apr. 1953. 3 refs.

Amenorrhoea is a symptom of some functional disturbance in the absence of a physiological cause. The response of the uterus to administration of oestrogens is not impressive and adequate therapy depends upon the discovery of the true cause of the amenorrhoea. The uterus, ovary, pituitary and mesencephalos form a complete system, in which physiological reactions determine the menstrual cycle.

In cases of organic origin, particularly in cases of primary amenorrhoea, it is possible to track down the site of pathology, but in functional amenorrhoea the cycle may be disturbed by hormonal stimuli which might be of cortical, adrenal or thyroid origin. Amenorrhoea of organic uterine origin may be associated with congenital hypoplasia or absence of the uterus and of the vagina. This may be confined to Müller's ducts in which case the ovaries may be normal. An extremely rare case of organic amenorrhoea of uterine origin may be associated with tuberculosis beginning before the menarche or may follow destruction of the endometrium after parturition, abortion, curettage, etc. In such cases, the ovary, pituitary and hypothalamus are normal and normal vaginal smears are obtained. Therapy is disappointing. The diagnosis is confirmed by the absence of bleeding after the administration of oestrogenic hormones. Amenorrhoea may occur even in the presence of a normal uterus which undergoes cyclical menstrual changes without actual haemorrhage. In such cases, it is possible for ovulation and pregnancy to occur.

Amenorrhoea of ovarian origin is more frequent. Failure of development is the prime cause. Absence of the ovary is recognized by the absence of secondary sexual characteristics. Most cases are of small stature and there is poor development in other organs. In such cases, there is a high urinary output of pituitary gonadotrophic hormones. The administration of progesterone as a test does not produce bleeding. The treatment is early and with prolonged administration of oestrogens it is possible to get some development of female characteristics. Less rare is hypoplasia of the ovary, associated with deficient numbers of primordial follicles. Characteristically, these patients are of normal stature but have poorly developed breasts and certain masculine features. The prognosis in such cases is poor and menstruation may be scanty, and associated with a late menarche and early menopause.

Amenorrhoea of secondary type may also be associated with large ovaries, yellow on cross section, due to persistence of corpora lutea or excessive luteinization. Menstruation is very irregular and there may be long periods of amenorrhoea. There is normal libido. The response to hormone preparations in therapeutic doses is disappointing and rarely results in establishment of a normal menstrual cycle. Infective diseases or tumours of the ovary rarely cause amenorrhoea.

Amenorrhoea of pituitary origin is associated with lack of development in the genitalia. A secondary form may follow a pregnancy, particularly when associated with haemorrhage, and is due to the disturbance of metabolism of the anterior pituitary.

Amenorrhoea of hypothalamic origin may follow encephalitis or severe cerebral injury. Functional amenorrhoea originating in a block of the pituitary-hypothalamic pathway is usually secondary and may be associated with emotional disturbance, anxiety, fear, starvation. Administration of oestrogenic hormones is followed by bleeding. There is a spontaneous return to normal menstruation with removal of the emotional stress. Another type of secondary amenorrhoea is associated with severe diseases such as pulmonary tuberculosis and diabetes. It may also be associated with mental diseases and epilepsy. There is often difficulty in establishing a correct diagnosis between organic and functional forms. Diagnosis depends on a careful examination of the general physical state, studies of basal temperatures, biopsies of the endometrium and vaginal smears, combined with test doses of oestrogens and progesterone. X-ray examination of the sella turcica and of the long

bones should be done. Estimation of the urinary gonadotrophic hormones is helpful but estimations of the oestrogenic levels, progesterone levels and ketosteroids are of no practical value. *Patrick Steptoe*

55. **Chiari-Frommel Syndrome.** (Sindrome de Chiari-Frommel.)

By M. SCHTEINGART and S. D. PROVENZANO. *Obstet. Ginec. Lat-amer.*, **11**, 76-81, Apr. 1953. 2 photomicrographs, 11 refs.

A case is reported of superinvolution of the uterus and amenorrhoea in an Argentine patient aged 18 years, following a delivery 4 years previously.

The authors in a historical summary state that J. B. Chiari in 1855 reported that among the gynaecological patients in a Vienna hospital between the years 1848 and 1855 there were 2 such cases as the authors now present. In 1882 Frommel reported further cases, which he regarded as an exaggeration of the normal process of involution of the uterus. Many such cases have been reported from various centres and most have been attributed to excessive lactation.

The case reported is that of a normal delivery in a 14-year-old patient: the baby was stillborn (no explanation given). The puerperium was complicated by pyrexia and bleeding, to the extent that a blood transfusion had to be given. Lactation was never allowed to develop. Amenorrhoea ensued (except for a scanty loss when hormones had been given), and frequent headaches were experienced.

Examination showed an apparently normal young woman; the hair was normal, and the breasts well developed. The cytology of the vagina was normal. Vaginal examination did not disclose any abnormality whatsoever, except that it was impossible to palpate the body of the uterus

Laparotomy was performed (reason not stated), and this revealed a uterus about the size of a large almond, bluish in colour with white streaks.

The ovaries and Fallopian tubes were normal, and all viscera freely mobile. A wedge-shaped biopsy was taken from the fundus of the uterus, and from the ovaries. Microscopical examination showed that the ovaries were functioning normally. The uterus, however, showed no evidence of endometrium, and the myometrium showed marked sclerosis of the interstitial tissue, and numerous arterioles with sclerosed walls and some hyalinization.

Prolonged lactation is cited as a cause in some cases—although, as the authors point out, wet nurses did not commonly develop this condition. The possible association of puerperal sepsis is mentioned. From the study of their own case, the authors suggest that the condition is purely a vascular degeneration confined to the uterus. *John F. Foulkes*

56. **Observations on Post-menopausal Bleeding.** (Consideraciones sobre la hemorrhagia genital postmenopausica.)

By A. D. BUENDIA and S. F. TEARE. *Obstet. Ginec. Lat-amer.*, **11**, 427-432, Oct. 1953. 9 tables, 9 refs.

An investigation into the causes of post-menopausal bleeding was carried out at the University Gynaecological Hospital of Santiago, Chile. Between the years 1942 and 1952, 488 post-menopausal patients (4·9 per cent of all cases) attended the hospital complaining of vaginal bleeding. (Post-menopausal bleeding is defined as bleeding occurring more than one year after the menopause.) All examinations were made first by biopsy of the cervix and endometrium, and then by curettage if the former did not disclose any cause.

The authors found that age was of no significance, except between the years of 45 and 50, when there was a predominance of epithelioma of the cervix, producing a malignancy rate of 64·1 per cent compared with 52·4 per cent in later years. No connexion was found between the incidence of malignancy and parity, nor the age at the onset of symptoms.

Studying the time interval between the first occurrence of bleeding and the consultation at hospital, the authors found that only 16 per cent came within the first 4 weeks, and of these 38·4 per cent were malignant: according to their table, it is observed that, as the interval becomes longer, so the percentage incidence of malignancy rises. When the interval exceeds 12 months, the incidence is 66·6 per cent.

Of the 488 patients investigated, the cause in 223 (45·6 per cent) was benign, the commonest cause (constituting 11·3 per cent) being functional bleeding, under which heading are included atrophic and proliferative endometria. The second commonest cause (contributing 10·5 per cent of the 45·6 per cent) was cervical polyp. No cases of stilboestrol withdrawal bleeding were found among the hospital patients.

Of the 54·4 per cent malignancy cases, carcinoma of the cervix contributed 40·2 per cent and carcinoma of the body of the uterus 11·2 per cent. Two instances of endometrial carcinoma were found in cases exhibiting hyperplasia of the endometrium. *John F. Foulkes*

57. **Physiological and Clinical Aspects of Conception.**

By E. T. TYLER. *J. Amer. med. Ass.*, **153**, 1351-1356, 12th Dec., 1953. 14 refs.

There is much that is still obscure in the mechanism of conception, and this paper attempts to correlate some of the known aspects of normal reproduction with the problems of clinical infertility. The physiology of spermatogenesis is discussed and followed by an account of the hostile factors which may be encountered in the female reproductive organs. Antibiotic treatment is recommended in certain types of cervicitis and the dangers of excessive cauterization are stressed. As a result of studies on approximately 4,000 semen specimens the writer concludes that pregnancy is highly unlikely when the sperm count remains below 20 million, and that counts of 60 million should be taken as the lower limit of normal.

Treatment aimed at increasing spermatogenesis is not very successful, and 21 men were treated by testosterone in sufficient doses to suppress spermatogenesis for long periods but not a single case showed the "rebound" to normal sperm production upon cessation of treatment.

From the practical standpoint the usefulness of temperature charts is limited. Apart from difficulties in interpretation, donor insemination only once in the

cycle has shown that conception can occur as long as 5 days before the temperature rise and up to 4 days afterwards. These conclusions were reached after reviewing 1,086 instances of artificial insemination.

Failure of implantation of the fertilized egg ("conception-less fertilization") may respond to treatment with large doses of progesterone and oestrogen. To reduce the inhibiting effect of this treatment upon gonadotrophic stimulation, chorionic gonadotrophin is also employed. Suggested daily doses are 15 mg. of progesterone and 1·5 mg. oestradiol 3-trimethylacetate intramuscularly and 1,000 I.U. chorionic gonadotrophin on alternate days in the second half of the cycle. The author concludes that, in specialized sterility practice today, it is unlikely that more than 1 out of every 3 couples with a true sterility problem can be helped, and this excludes patients who prematurely seek advice and receive therapy long before there is any need for it. *D. W. James*

58. **The Dynamic Significance of Vaginal Lubrication to Frigidity.**

By E. GERGLER and W. S. KROGER. *West. J. Surg.*, **61**, 711-716, Dec. 1953. 27 refs.

The authors, from the Department of Obstetrics and Gynaecology, Chicago Medical School, describe the anatomy and physiology of the secretory glands of the labia and vestibule and stress the difference in purpose between secretion in the female and ejaculation in the male. They discuss various theories about female orgasm and discuss the psychological implications of sex functions in the female. They conclude that frigidity in the female is primarily a psychological upset and is very rarely due to organic disease.

[The theories discussed are nothing if not interesting. Most clinicians in this country will probably agree with the conclusions but not with the argument which leads to them. The paper is worth reading in spite of this.]

D. C. A. Bevis

59. **The Growth Pattern of Cervical Cancer.**

By S. B. GUSBERG, S. A. FISH and YIN-YING WANG. *Obstet. Gynec.*, **2**, 557-561, Dec. 1953. 3 figs., 4 refs.

This study is based upon 91 cases of carcinoma of the cervix treated surgically at the Sloane Hospital, and comes from Columbia University, New York. Eighty-two patients with Stage I and Stage II carcinoma of the cervix were subjected to radical (Wertheim) hysterectomy, while 9 lesions were found accidentally at total hysterectomy. Each specimen was fixed, and the gross extent of the tumour was mapped on diagrams, which are shown in the illustrations. Microscopic extension was also determined. There were 84 epidermoid carcinomas and 7 adenocarcinomas. Twenty-seven of 72 cases showed intra-epithelial carcinoma at the margins of the lesions. There was pelvic node involvement in 10·4 per cent Stage I and 31·2 per cent Stage II cases. The total area involved in the spread of the cancer was mapped out for each tumour in 73 cases, and none showed involvement of the portio alone. There was always spread into the cervical canal, and when the stroma of the canal was involved, spread seemed to be by concentric expansion. The parametrium was frequently reached before the portio.

The authors point out that these findings underline the importance of canal biopsy and curettage in evaluating a cervical lesion, particularly an intraepithelial carcinoma. The incidence of parametrial invasion and node metastases was smaller in the fungating type of lesion than the ulcerating type. *J. G. Dumoulin*

60. **Traumatic Cyst of the Spleen, Simulating an Ovarian Tumour.** (Cisti traumatica della milza simulante un tumore ovarico.)

By E. WIENINGER. *Riv. Ostet. Ginec.*, **8**, 145-149, Mar. 1953. 2 figs., 14 refs.

In the University of Graz, in the years 1946-1952, 2,350 laparotomies were performed, including two cases in which a pre-operative diagnosis of an ovarian cyst proved to be erroneous. In one of these cases, there was a mesenteric cyst, cases of which have been previously described. In the second case, the author has been unable to find a report of a similar case in the literature.

The patient was a gravida-4, aged 28, who was referred with a diagnosis of pedunculated ovarian cyst. She had complained of pain in the left iliac fossa of a few days' duration. There were no menstrual disturbances. Bimanual examination revealed a cystic mass in the left side of the pelvis; this appeared to be separate but close to a normal left ovary. A pre-operative diagnosis of a parovarian cyst was made. Laparotomy was performed and there was found to be a blue elastic cyst about the size of a fist in the left side of the pelvis. The uterus, tubes, and ovaries, were quite normal. The cyst was adherent to the omentum but not attached to the pelvic organs. Beneath the omentum there could be seen an enlarged firm prolapsed spleen. This was in the lower left abdomen and almost reaching the pelvis. The cyst was found to be arising from the spleen and covered with a thin shell of splenic capsule. The omental adhesions were divided and splenectomy performed.

The pathological report described the mass as a thin smooth cyst arising from the convex surface of the spleen, containing a haemorrhagic fluid, the internal surface being covered with yellow-grey necrotic nodules. The cyst appeared to arise from the splenic capsule which was very much thickened. The wall of the cyst was of thickened connective tissues, disposed in several layers, showing paucity of cells. The pathological diagnosis made was a traumatic cyst of the spleen.

Interrogation of the patient after recovery from the operation revealed a history of an injury three years before, when she had been kicked in the left hypochondrium.

Although enlargement of the spleen into the pelvis is not uncommon, it is unusual for a diagnosis of prolapse of the spleen to be made. In this case, the author considered that elongation of the splenic pedicle was probably due to the weight of the cyst and the lack of resistance in the abdominal muscles, which were of poor quality. Cysts of the liver, kidney, omentum, or of an echinococcal origin have been confused with ovarian cyst, but this particular case appears to be rare and

unusual. Splenectomy is probably the treatment of choice for such a case. *Patrick Steptoe*

61. Vesicovaginal Fistulae. Review of 100 Consecutive Cases.

By J. C. MOIR, *Lancet*, **1**, 57-61, 9th Jan., 1954. 4 tables, 5 figs., 6 refs.

The author records his experiences with 100 consecutive cases of vesicovaginal fistulae. The cause of these fistulae was obstetrical in 36 cases and gynaecological in 64, when the injury usually resulted from extensive or difficult pelvic operations. No fistula caused by active carcinoma is included in the series. The duration of the fistula varied from 7 to 32 years and 75 of the 100 patients had had one or more previous operations before coming under observation. Closure of the fistula was obtained at the first operation in 82 cases, at the second operation in 13, and at the third operation in 2 cases. In 3 patients closure of the fistula was obtained by simple drainage. The author points out that the presence of dense fibrous tissue is the chief cause of difficulty in fistula repair and that fistulae caused by radium are particularly difficult to treat. In cases where there is complete destruction of the urethra, of which there were 12, the physiological results were not always good owing to defective sphincteric control. In 4 of these 12 cases transplantation of the ureters into the colon was advised and carried out in 3, the only cases in which this operation was carried out. One of these patients died, the only fatality in the whole series. All the fistula operations were dealt with by the vaginal route. The essential feature of the operation is the establishment of broad raw surfaces in the combined bladder and vaginal walls, which are sutured with either silver wire or monofilament "Nylon" No. 5 size. Bladder drainage by suction is carried out for 14 days and the sutures removed on the 21st day.

H. H. Fouracres Barns

62. Management of Vesicourethral Dysfunction in Women.

By R. B. CARSON. *J. Amer. med. Ass.*, **153**, 1152-1155, 28th Nov., 1953. 7 refs.

This paper reviews the symptoms of 1,000 women seen in private urological practice. 52·9 per cent of these were found to have lower genito-urinary tract dysfunction commonly due to some form of cystitis or urethritis. A general and neurological examination should precede the urological examination which includes bimanual palpation of the urethra, trigone, and ureters. In many cases it is necessary to proceed further to inspection of the bladder and intravenous or retrograde pyelograms.

The author suggests that chronic urethritis is the result of urinary stasis in the urethral canal between the meatus and the vesical neck, and that infection is not a common cause. Stricture may be associated with it and so also may extrinsic obstruction due to urethrocele or sliding urethra. Treatment should be by gradual urethral dilatation, and, if plastic surgery is considered necessary, it should include (1) immobilization of the urethra, (2) elongation of the urethra, and (3) elevation and support of the vesical floor. In this series of cases only 5·9 per cent suffered from cystocele and 1·5 per cent from urethrocele.

The treatment of chronic cystitis, present in 28·9 per cent, is discussed. For bladder-neck contraction transurethral resection with follow-up dilatation gives the best results. Urethral diverticula are often overlooked and require surgical eradication of the sac. The paper concludes with a description of the anatomy of the urethra and bladder, and an account of the physiology of micturition as observed radiologically and by cystourethroscope. *D. W. James*

63. Chronic Bladder Irritation in Females.

By H. A. O'BRIEN and J. D. MITCHELL, JNR. *J. Amer. med. Ass.*, **153**, 1149-1152, 28th Nov., 1953.

An analysis of the records of 200 consecutive patients in urological practice presenting symptoms of bladder disturbance showed that in 75 per cent symptoms resulted from lesions in the urethra and trigone. The greatest number of cases presented between the ages of 30 and 60, indicating the importance of trauma as an exciting factor. The symptoms of these patients fell into three main groups, namely, urinary, referred pain, and nervousness. The authors consider that nervousness is frequently the result of bladder irritation rather than the cause. 65 per cent had normal urines although the basic lesion was infection of unknown origin in the urethra and trigone.

The commonest pathological finding was urethral stricture, but granular urethral mucosa, papillary masses, trigonitis and cervicitis were also found in many cases. Antibiotics and antiseptics were found to be useful only in those cases with acute cystitis. Dilatation of the stricture to No. 30 French catheter cured 26 per cent of the cases without further treatment. Fulguration through an endoscope using a very light current was used to destroy granular masses in the urethra, preceded by dilatation when necessary. 2·5 per cent of the patients had bladder neck obstruction and were treated by transurethral resection with fair results. After a 3-year follow-up 184 patients were contacted and 75 per cent were completely relieved. An additional 18 per cent were comfortable and in 5 per cent treatment had failed. The authors conclude that dilatation of strictures and destruction of infected tissues in the urethra and trigone are the most effective treatment in this distressing condition.

D. W. James

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